An Exploration of Prescribing and Administration Practices in Care Homes using Big Data

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By

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ABSTRACT

BACKGROUND

The care home population is recognised as being a high-risk group with respect to potential harm from medicines. However, as medicine administration records (MAR) have traditionally been recorded on paper, examination of medicines use in care homes has been challenging, time-consuming and resource-intensive.

METHODOLOGY

This thesis explored the potential for using a database of secondary, pseudonymised electronic MAR (eMAR) data for furthering research and enhancing clinical practice in England, using exploratory analysis of dopaminergic medicines as a case study. The source database was interrogated, and data processed using SQL code. Statistical testing and figure creation was conducted using R code and Microsoft Excel. Analysis included assessment of the prevalence of dose omissions and a comparison of the standard approach for assessing the timeliness of levodopa administration by the time difference between the required and administered times (dosing accuracy) to a novel approach comparing the actual and expected time gaps between doses (dosing precision), using Bland-Altman quantile regression plots.

RESULTS

9,082 individuals across 310 care homes were identified following data pre-processing. 375 and 319 individuals had a record of dopaminergic or levodopa medicines, respectively. 2.15% of 40,187 required dopaminergic medicine doses examined were omitted, most commonly due to the resident declining. 19,008 of 35,279 levodopa doses administered were within 30 minutes of the required time. However, little concordance was seen between measures of dosing accuracy and dosing precision.

CONCLUSIONS

Harnessing eMAR data may facilitate large-scale research, strengthen clinical monitoring procedures and enable the development of complex clinical interventions. The development and use of data assets should be prioritised, alongside continual monitoring and improvement of data quality.

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COMMONLY USED ABBREVIATIONS

ADL:	Activity of Daily Living
BNF:	British National Formulary
CCG:	Clinical Commissioning Group
CHUMS:	Care Homes Use of Medicines Study
COMT:	Catechol-O-Methyltransferase
CQC:	Care Quality Commission
dm+d:	Dictionary of Medicines and Devices
eMAR:	Electronic Medicines Administration Record
LED:	Levodopa Equivalent Dose
MAE:	Medicine Administration Error
MAOB:	Monoamine Oxidase B
MAR:	Medicines Administration Record
NHS:	National Health Service
NICE:	National Institute for Health and Care Excellence
OGL:	Open Government Licence
ONS:	Office for National Statistics
PD:	Parkinson's disease
PIM:	Potentially Inappropriate Medicine
SAIL:	Secure Anonymised Information Linkage
SALT:	Short and Long Term Support
SSMS:	SQL Server Management Studio
VMP:	Virtual Medicinal Product
VTM:	Virtual Therapeutic Moiety

1 BACKGROUND

1.1 CARE HOMES

Care homes, offer accommodation and 24-hour support with Activities of Daily Living (ADLs) to individuals, with (i.e. nursing homes) or without (i.e. residential homes) 'round the clock' nursing care (Competition & Markets Authority 2017, p. 21). The majority of care homes are run by independent for-profit and charitable providers (Competition & Markets Authority 2017, p. 7). Individuals may require care home services for a variety of reasons (e.g. physical and cognitive impairments; mental health conditions; and learning disabilities) (NHS Digital 2020) and admissions may be short-term (e.g. for respite care or rehabilitation), or long-term (Competition & Markets Authority 2017), and self-funded or publicly funded (Competition & Markets Authority 2017, p. 7). All care homes in England must be registered with the Care Quality Commission (CQC), who regulate and inspect care homes to ensure they provide safe and effective care, are well-led and deliver high-quality services (Care Quality Commission [no date]); this includes checking that medicines are used safely (Care Quality Commission 2017). In January 2021, the CQC Directory of services listed 456,098 registered beds across 15,342 registered care homes providing care to adults in England (Care Quality Commission 2021a).

1.1.1 Individuals living in care homes

Individuals living in care homes are more likely to be older, and female. Analysis of 2011 census data found 82.5% of individuals living in care homes to be aged 65 years or over (Smith 2014) and around 90% of all Adult Social Care beds recorded in the CQC Directory of services in January 2021 provided care for older adults (Care Quality Commission 2021a). Furthermore, there has been an observed shift to an older demographic over time, with 56.5% of older adults (aged 65 years and over) living in care homes reported to be aged 85 years and over in the 2001 Census compared to 59.2% in 2011 (Office for National Statistics 2003,2013; Smith 2014). Meanwhile, there exists an approximately 3:1 ratio of women to men in care homes according to the 2011 Census (Office for National Statistics 2013), although this imbalance appears to be slowly reducing over time, from 3.3:1 in 2001 to 2.8:1 in 2011 (Smith 2014).

Among the general population, a trend towards an ageing population has been demonstrated (Coombs et al. 2019). With this, one would expect an increase in the number of individuals requiring care home services. However, despite the ageing of the population, the Office for National Statistics (ONS) reported little increase in the number of individuals aged 65 years and over living in care homes in the UK between the 2001 and 2011 Censuses (Smith 2014). A similar picture is seen in Grant Thornton's 2018 market report on care homes for the elderly, which described a decline in the absolute number of older adults living in care homes by 4.4% between 2001 and 2016 (Smith et al. 2018). Despite this, approximately 15% of individuals aged 85 years and over live in a care home (Smith et al. 2018), representing a significant proportion of this population. There is also some evidence that the rate of decline in the proportion of older adults requiring care home support is slowing which, coupled with continued ageing of the general population, may lead to an increase in the total number of older adults living in care homes in future years (Smith et al. 2018).

1.1.2 Reasons for needing care support

Individuals may require care support for various reasons. Figure 1.1 shows the type of primary support reasons for individuals needing accommodation in care homes in the financial year of 2019/2020 (NHS Digital 2020). As can be seen, the health and care needs of younger and older adults residing in care homes is quite different. For example, clinical conditions associated with a higher likelihood for requiring long-term care that more commonly affect individuals over the age of 65 years include those affecting mobility such as Parkinson's disease (British Geriatric Society 2007; Koller et al. 2014; Safarpour et al. 2015; Doyle 2018), and those affecting cognition, in particular dementia (Gordon et al. 2014; Koller et al. 2014; Prince et al. 2014, pp. 27-32). These are less prevalent in younger adults, who are more likely to require extra support due to learning disabilities or mental health conditions (NHS Digital 2020). As a result of these differences, it is appropriate to examine older and younger aged care home populations separately.

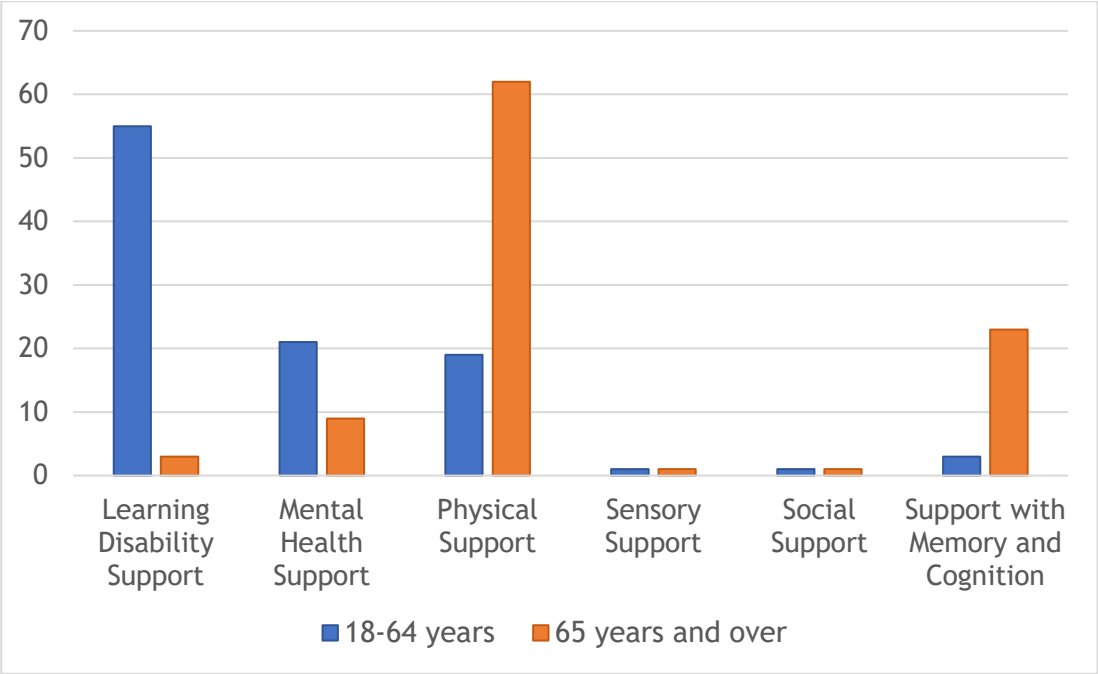

Figure 1.1: Prevalence of type of primary support reason recorded for individuals in nursing and residential homes in the 2019-20 Short and Long Term Support (SALT) collection. Data provided by NHS Digital (NHS Digital 2020) and used under the Open Government Licence for use of public sector information (The National Archives 2021).

1.2 Older adult care home population

As described previously, there is a disparity in the most common reasons for requiring care between older and younger adult care home populations. Moreover, there are several other health-related features more commonly associated with older adults within both the care home and community settings. These are outlined in this section.

1.2.1 Geriatric syndromes, multimorbidity and frailty

The association between older age and care home residency (Smith 2014) may be in large part due to confounders of multimorbidity and frailty. Multimorbidity, commonly defined as two or more concomitant clinical conditions (co-morbidities) (van den Akker et al. 1998; Barnett et al. 2012; Yarnall et al. 2017; Soley-Bori et al. 2021) is more prevalent in older age groups (van den Akker et al. 1998; Barnett et al. 2012) and care home residents (Smith et al. 2015), with a mean of 6.2 clinical conditions per individual reported in a previous study examining the latter group (Gordon et al. 2014).

Frailty is a type of geriatric syndrome, a group of multifactorial conditions more prevalent in older adults. It is a syndrome of increased vulnerability associated with a multiorgan deterioration leading to symptoms such as weight loss, weakness, and exhaustion (Chen et al. 2014; Kojima et al. 2018), which has been found to be a predictor of nursing home placement (Clegg et al. 2016 described in Kojima et al. 2018). Other geriatric syndromes include falls, incontinence, and delirium (Inouye et al. 2007).

Both multimorbidity and frailty have been found to be associated with adverse outcomes, including a reduced quality of life (Marengoni et al. 2011; Kojima et al. 2016; Makovski et al. 2019), functional decline (Marengoni et al. 2011; Kojima 2017; Makovski et al. 2019), and increased mortality (Nunes et al. 2016; Kojima et al. 2018). This may in part explain the greater mortality and emergency hospitalisation rates seen in individuals living in care homes compared to those living in the community (Smith et al. 2015), with previous research finding a 1-year mortality of 26.2% among older adults living in care homes, compared to 3.3% in the community (Shah et al. 2013).

1.3 MEDICINES USE IN CARE HOMES

1.3.1 Polypharmacy and Potentially Inappropriate Medicines (PIM) use

Polypharmacy is a term use to describe the concurrent use of multiple medicines. It is most commonly defined quantitatively as an individual receiving five or more medicines, however there is considerable variation seen in the literature with respect to this (Jokanovic et al. 2015; Masnoon et al. 2017). Previous studies have found individuals in care homes are prescribed an average of between 8 and 9 medicines (Barber et al. 2009; Szczepura et al. 2011; Shah et al. 2012; Gordon et al. 2014), compared to a mean of 4.9 for community-dwelling older adults in England and Wales (Shah et al. 2012). However, considerable variation in the proportion of individuals experiencing polypharmacy in care homes has been seen. For example, a recent systematic review reported between 38.1 and 91.2% of individuals were prescribed five or more medicines (Jokanovic et al. 2015). Polypharmacy in older adults has been found to be associated with an increased risk of hospitalisation and medicine issues, including potentially

inappropriate prescribing, and poor compliance and adherence (Davies et al. 2020).

Despite this, there is a recognition in healthcare guidance that not all polypharmacy is inappropriate and therefore there should be an attempt to differentiate appropriate polypharmacy from problematic polypharmacy (Duerden et al. 2013, p. ix; National Institute for Health and Care Excellence 2017a; Royal Pharmaceutical Society 2019). In the research literature, this distinction can be evidenced through the study of Potentially Inappropriate Medicines (PIM) use. Many tools have been developed to help identify PIMs. The most commonly used in the research literature for identifying PIMs in care homes is the United States (US) Beer's criteria® (American Geriatrics Society Beers Criteria® Update Expert Panel 2012,2019) followed by the Screening Tool of Older People's Potentially Inappropriate Prescriptions (STOPP) criteria (Gallagher et al. 2008; Moody et al. 2014, pp. 17-20; Morin et al. 2016; Wang et al. 2018). Some of the reasons for the use of a medication being considered potentially inappropriate are outlined in Figure 1.2.

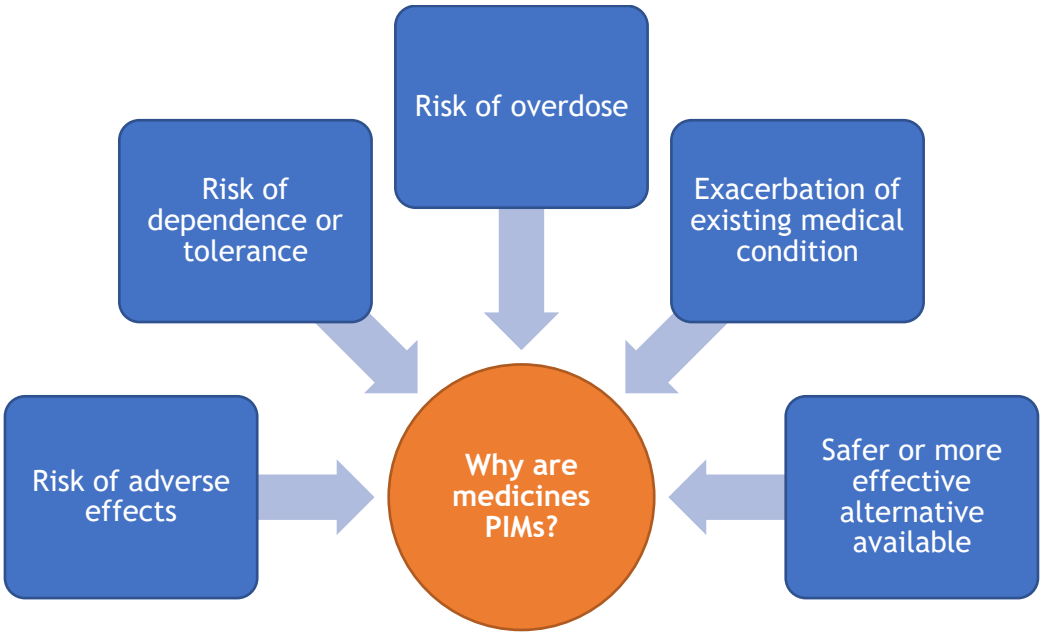

Figure 1.2: Reasons why a medicine may be considered potentially inappropriate (Gallagher et al. 2008; American Geriatrics Society Beers Criteria® Update Expert Panel 2012; Moody et al. 2014, pp. 17-20; American Geriatrics Society Beers Criteria® Update Expert Panel 2019)

A positive correlation has been found between PIM use and polypharmacy (Storms et al. 2017; Davies et al. 2020) and, as with polypharmacy, PIM use has been found to be more prevalent in care homes than in the community. For example, studies suggest that around 33-61% of care home residents receive at least one PIM compared to 21-31% in the community (Shah et al. 2012; Thomas 2016; Storms et al. 2017). Within the care home setting, there does not appear to be a significant different in the rate of PIM prescribing between residential and nursing homes in England (Shah et al. 2012). However, it is worth noting the differences in implementation of the tools in primary research, given some studies omit criteria within the tools as necessary clinical information if often unavailable (Thomas 2016; Storms et al. 2017). As with polypharmacy, a recent systematic review and meta-analysis found PIM use to be associated with an increased risk of hospitalisation (odds ratio 1.44, 95% confidence interval 1.33 – 1.56), as well as adverse drug reactions (odds ratio 1.27, 95% confidence interval 1.20 – 1.35), but no statistically significant association was found for mortality (Xing et al. 2019).

1.3.2 Medicines administration

Medicines management is "a system of processes and behaviours that determines how medicines are used" (National Prescribing Centre 2002 as described in National Institute for Health and Care Excellence 2015). This includes processes for ordering, storing, administering, recording and review of medicines to ensure that these are used safely and effectively (National Institute for Health and Care Excellence 2014b), and accounts for a significant proportion of care staff time (up to 50%) (Alldred et al. 2009, p. viii). Care home staff involved in the management of medicines should be adequately trained, and the procedures for managing medicines should be outlined in the care homes' policy (National Institute for Health and Care Excellence 2014a; Care Quality Commission 2017). In England, medicines management is monitored by the CQC during inspections of care services, under the Key Line of Enquiry S4: "How does the provider ensure the proper and safe use of medicines?" (Care Quality Commission 2017).

Individuals living in care homes may self-administer medicines or have these administered by care home staff (National Institute for Health and Care Excellence 2014b). No research outlining the prevalence of self-administration in care homes in the UK could be found, although evidence for this may be available locally through audits (National Institute for Health and Care Excellence 2015a). However, it has previously been reported that medicines within care homes is typically managed by staff during 3-4 medicine rounds at regular intervals during the day i.e. morning (8 am), lunch (12 pm), afternoon (4 pm) or evening (8pm) / night (10 pm) (Alldred et al. 2009, p. 19; Al-Hamadani 2018, p. 19). These may be long, taking 2 or more hours (Alldred et al. 2009, p. 19). Medicines may be administered from either a pre-packaged multi-dose systems (MDS; where medicines are repackaged into separate compartments for each administration round), or original medicine packs, or a combination of both (Alldred et al., pp. 11-15; Al-Hamadani 2018, pp. 18-19). Staff administering medicines should be trained to do so (Care Quality Commission 2017). In residential homes, this is undertaken by care staff, who typically hold a National Vocational Qualification (NVQ), while in nursing homes these may be administered by nurses, with or without the assistance of care staff (Royal College of Nursing 2021).

1.3.2.1 Medicine Administration Records (MAR)

Under the Health and Social Care Act 2008 (Regulated Activities) Regulations 2014, care providers are required to make accurate records of medicines use for all individuals for whom they provide medicines related support; these records must be maintained for at least 8 years following the end of the individuals' time at the home (Care Quality Commission 2021b). These records should contain the details of all medicines that may be used by the resident, either prescribed or over-the-counter (otherwise known as homely remedies), along with information about the resident, including their full name, date of birth, and any allergies (Care Quality Commission 2021b). The date and times, or time of day, at which doses are administered should be recorded (Care Quality Commission 2021b). Finally, when a staff member attempts to administer a medicine, administration should be signed for by

the staff member and, where the medicine is not given, a reason for this should be recorded (Care Quality Commission 2021b).

1.3.2.1.1 Electronic Medicine Administration Records (eMAR)

Medicine administration records (MAR) are generally maintained using paper charts held within the care home, with a new chart completed for each 28-day cycle for each resident (Alldred et al. 2009). These may be produced by either the dispensing pharmacy or care home staff (Alldred et al. 2009). However, in recent years, there has been increasing interest in the potential benefits of using digital technology in the delivery of health and social care services (NHS England et al. 2014, pp. 4-5; Topol 2019). In care homes, this has seen the implementation of electronic MAR (eMAR), representing the digitisation of the medicines administration record (Al-Hamadani et al. 2015; Department of Health and Social Care 2021; QA Research 2021). Despite this, with estimates of around 30%, the proportion of care homes using eMAR remains low (Department of Health and Social Care 2021; QA Research 2021, p. 13).

There are several types of eMAR available in the UK (CASPA Care [no date]). The principle of digitisation of the medicine records is universal, however specific features and user interface designs vary. Medicines may be administered using multi-compartment compliance aids (Care Meds [no date]) or original packs (Digital Social Care [no date]). For some systems, barcodes are produced by the dispensing pharmacy, which are then scanned by staff within the care home during medicines management processes (MED e-Care [no date]; Omnicell™ [no date]a; Atlas eMAR [no date]a). This facilitates stock tracking (Omnicell™ [no date]a; Atlas eMAR [no date]a) and safety alerts, for example where an incorrect medicine pack is picked in error (ATLAS eMAR [no date]a; Omnicell™ [no date]b). Other features eMAR systems may have include a link with the dispensing pharmacy (VCare [no date]a; MED e-Care [no date]; ATLAS eMAR [no date]a) or GP practice (ATLAS eMAR [no date]b); reporting capabilities (VCare [no date]a; (Omnicell™ [no date]a; ATLAS eMAR [no date]a; MED e-Care [no date]; Care Meds [no date]); and integration with care planning records (VCare [no date]a; ATLAS eMAR 2019; Omnicell™ [no date]c).

There are many case studies in the grey literature outlining the benefits experienced by eMAR users within care homes in the UK (Zuzarte [no date]; (VCare [no date]b; Elizabeth Finn Homes [no date]; Digital Social Care [no date]; Omnicell™ [no date]d; ATLAS eMAR [no date]c). However, recent work by researchers at the University of Nottingham has examined the barriers to sustaining the use of an eMAR system following its implementation within the care home setting. In this study, interviewees working in care homes identified barriers across four themes – infrastructural (e.g. unreliable wireless internet connection); implementation team (e.g. attitude towards system users); operational (e.g. lack of access to system data for visiting healthcare professionals); and system user (e.g. staff turnover). (Karsan et al. 2021).

Research evaluation of eMAR within UK care homes includes studies conducted by researchers at Cardiff University, examining the safety, efficiency and waste associated with medicines management pre- and post-implementation of a barcode-enabled eMAR system. The researchers found 21 of the 23 medicine error types associated with medicines management were eradicated; time spent by on medicines management activities was reduced by 17.4% and medicines waste being returned from the care homes was reduced by 55% following implementation of the barcode-enabled eMAR (compared to traditional paper-based MAR charts) (Al-Hamadani et al. 2015, pp. 16-29; Smith 2016). Another study by researchers at Coventry University found the use of safety alerts to be associated with an increased staff awareness of 'near miss' medicine errors following the introduction of a bar-code enabled eMAR system. Only one staff member surveyed described overriding the safety alerts, using clinical judgement to administer medicines shortly before the required time. The use of the eMAR system was also found to be associated with fewer interruptions during medicine administration rounds (Wild et al. 2016). However, it should be noted that results for research examining one eMAR may not be transferrable to other eMAR systems where there are significant differences in design, and the availability of research evidence may be impacted by publication bias.

1.3.3 Medicine errors

Medicine errors occur where a breakdown in any part of the medicines management process causes, or has the potential to cause an individual harm (Aronson 2009). Medicine errors have been classified in several ways. Psychological theory classifies errors based on the cause of failure, where knowledge- and rule-based errors (mistakes) occur due to failures of planning, while action-based errors (slips) and memory-based errors (lapses) occur due to failures in execution (Aronson 2009). Medicine errors may also be classified by the type of error that has occurred, such as wrong administration route or wrong medicine; by the part of the medicines process in which the error occurs (i.e. prescribing, dispensing, monitoring or administration); or by the severity of harm that has or may occur as a result (World Health Organisation 2016, p. 4). These classifications may be used either alone or in combination (World Health Organisation 2016).

The seminal study examining the occurrence of such errors in care homes is the Care Homes Use of Medicines Study (CHUMS) (Alldred et al. 2009, pp. iv-vi; Barber et al. 2009). In this prospective study, clinical pharmacists explored the prevalence of medicine errors in 256 residents across 55 care homes in England (Alldred et al. 2009, pp. iv-vi). The researchers observed errors rates of 8.4% for medicines administration, 8.3% for prescribing, 14.7% for monitoring and 9.8% for dispensing (Alldred et al. 2009, pp. iv-vi). CHUMS is valuable in providing research evidence on how medicines are being used in the care home setting in England, where this had previously been lacking. However, notable limitations include a short observation period. For example, only two medicine administration rounds were observed (Alldred et al. 2009; Barber et al. 2009). Furthermore, not all residents within the homes studied were included, although a random sample was taken in an effort to reduce bias as a result of this (Alldred et al. 2009; Barber et al. 2009).

1.3.3.1 Medicine Administration Errors (MAEs)

Medicine Administration Errors (MAEs) are a type of medicine error occurring during the administration stage of the medicines management process (Barber et al. 2009). Medicines should be administered by care home staff in

line with the 6 rights of medicines administration i.e. “right resident, right medicine, right route, right dose, right time and right to refuse” (National Institute for Health and Care Excellence 2014a,2020). MAEs occur when there is a failure to administer a medicine in line with these six rights, or in accordance with medicine administration policies and/or the prescriber’s instructions (Keers et al. 2013).

MAEs have been found to affect the majority of care home residents. In the CHUMS study, 57% of individuals were exposed to at least one MAE (Alldred et al. ; Barber et al. 2009). In another study of potential MAEs in 345 residents across 13 UK care homes an even higher rate of exposure to MAEs was seen (90%) over the 3-month study period (Szczepura et al. 2011). However, a lower error rate was reported (1.2% vs 8.4% in CHUMS (Alldred et al. 2009; Szczepura et al. 2011)).

Differences have been seen with respect to the type of MAEs reported. While Szczepura et al. found three main categories for potential MAEs of wrong time, wrong resident and attempts to administer discontinued medicines (Szczepura et al. 2011), CHUMS found 70% of all errors were a result of either dose omissions (50%) or wrong dose (20%) (Barber et al. 2009). A possible cause for these differences may be the different types of MAR used. Paper charts were used in CHUMS (Barber et al. 2009). However, barcode-enabled eMAR was used in the study by Szczepura et al., with most of the potential MAEs identified prevented through the eMAR alert system (Szczepura et al. 2011).

1.3.3.1.1 Dose omissions

Dose omissions are a type of MAE where a prescribed dose is not given. This may occur for many reasons, including the individual declining the dose; a lack of stock availability; and being withheld on the basis of clinical judgement (Lawler et al. 2004; Munzner et al. 2012; Rostami et al. 2019; Garratt et al. 2020). However, there is inconsistency on the inclusion criteria of dose omissions in previous studies of prevalence. For example, CHUMS excluded dose omissions where clinically withheld, the individual was absent, or the individual declined the dose (Alldred et al. 2009). Similarly,

some studies have classified dose omissions into valid and non-valid reasons. However, while there is consensus on clinically withheld doses being a valid reason for omission, there is variability in the classification of other reasons, for example an individual declining, or being asleep or absent (Munzner et al. 2012; Rostami et al. 2019). Finally, gaps in the MAR chart may also occur as a result of either a failure to record the reason for non-administration or failure to sign for the administration (Lawler et al. 2004; Al-Hamadani et al. 2015).

Although a greater risk of dose omission has been found during transition of care (i.e. at the time of entry to a care home) (Desai et al. 2011 and Pronovost et al. 2003 as described in Lane et al. 2014), they may occur at any time during residency. Previous research has found that, where studied for an entire year, all care home residents experienced at least one omission (Garratt et al. 2020). Furthermore, there have been reported cases of individuals in care homes having a medicine omitted for the entirety of a 28-day medicine cycle (Al-Hamadani 2018, p. 132).

As outlined above, dose omissions were the most common reason for MAEs in care homes in CHUMS (Alldred et al. 2009; Barber et al. 2009). Excluding omissions due to the resident declining the dose, or where clinically withheld, 57 of 1380 doses (4.13%) were reported to be omitted (Alldred et al. ; Barber et al. 2009). A similar rate was seen in a study of dose omissions in 11,015 residents across 374 New Zealand care homes using de-identified eMAR records (3.59%) (Garratt et al. 2020). However, a higher prevalence of doses omissions has been seen in US skilled nursing facilities (7%) (Barker et al. 2002).

However, these studies report the prevalence of dose omissions as an aggregate of all medicines. This is notable as the medicine type affects the potential risk of harm associated with dose omission (Rehman 2010; Graudins et al. 2015). In one study providing details of the most commonly omitted medicines, this included paracetamol and several types of laxatives (Garratt et al. 2020). Meanwhile, a study examining MAEs for PIMs found dose omissions to be the most common reason for error (Al-Hamadani 2018). For

dose omissions of short-course medicines, antibiotics are frequently implicated (Garratt et al. 2020); these accounted for 38.9% of MAEs for antibiotics in Welsh care homes (Al-Hamadani et al. 2017). Furthermore, little research examining the reason for omission in care homes was identified. One study was identified, which reported 'not administered' was selected for around a half of omissions (Garratt et al. 2020). The researchers suggest these may have been for reasons such as supply issues or resident absence that were not captured in separate categories by the eMAR system being used for the study. The most common reason after this was refusal (34.6%), followed by withheld (15.5%) (Garratt et al. 2020). Together, these findings suggest that medicines administration errors are a common occurrence in care homes, although the clinical consequences of such errors remains underexplored.

1.4 USE OF EMAR DATA

As previously described, the use of eMAR has been reported to demonstrate a range of benefits, including improving safety and reducing medicines waste (Al-Hamadani et al. 2015). Another advantage of digitisation of medicine records is the ability to remotely access such records. With paper MAR charts, obtaining data for clinical monitoring or research purposes is challenging, often requiring travel and access to the care home, and a considerable burden of work for staff to extract data into a useable format for analysis. As a result, previous UK-based research on medicines use in care homes has typically relied on either small to medium sample sizes where data is collected directly from the care home (Alldred et al. 2009; Barber et al. 2009; Al-Hamadani 2018); or the use of postcode data and read-code analysis to identify care homes within GP records for prescribing level analyses (Shah et al. 2010; Shah et al. 2012,2013; Smith et al. 2015). UK studies identified that have made use of eMAR records to examine medicines use in care homes include the exploration of MAEs by Szczepura et al, as described previously (Szczepura et al. 2011); and an examination of antipsychotic use (Szczepura et al. 2016).

Internationally, along with the analysis of dose omissions in New Zealand described above (Garratt et al. 2020), several studies conducted in the United States (Berry et al. 2016; Aspinall et al. 2019; Lally et al. 2021) and Australia (Pont et al. 2018; Lind et al. 2019a; Lind et al. 2019b) were also identified. The use of eMAR data in these has facilitated the analysis of large sample sizes of up to 24,869 residents (Aspinall et al. 2019). A range of issues have been studied, including the use of medicines for managing dementia symptoms (Lind et al. 2019a); the association between central nervous system medicine use and falls and/or hip fracture (Aspinall et al. 2019) (Berry et al. 2016); polypharmacy and antipsychotic use (Pont et al. 2018); concurrent use of diuretics, Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARBs) and Proton Pump Inhibitors (PPIs) in individuals being administered Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (Lind et al. 2019b); and the association between SARS-CoV-2 30-day mortality and diabetes medicine use (Lally et al. 2021).

Beyond research, the ability to remotely examine large numbers of geographically dispersed care home residents may be beneficial in clinical practice, for example to aid in identification of potentially inappropriate medicines use, as well as for monitoring the quality and safety of services. This may include the introduction of computerised clinical decision support systems (CCDS[2]) (Marasinghe 2015). A systematic review examining the use of these in the care home setting suggests that CCDS may reduce the risk of harm amongst care home residents. However, research evidence remains scarce, with only seven primary studies identified (Marasinghe 2015).

1.4.1 Time-sensitive medicines

Digitisation of medicine management processes also allows for more comprehensive recording that may be challenging using paper-based records alone. For example, time-stamped records allow precise recording of the time at which medicines are administered. Time-stamped may prove

[2] Computerised clinical decision support systems (CCDSS) provide advice to healthcare professionals on potentially inappropriate medicines prescribing. Marasinghe, K. M. 2015. Computerised clinical decision support systems to improve medication safety in long-term care homes: A systematic review. *BMJ Open* 5(5), p. e006539. doi: http://dx.doi.org/10.1136/bmjopen-2014-006539

beneficial for clinical monitoring and research for time-sensitive medicines. For such medicines, delays in administration may negatively impact the individual (Rehman 2010; Graudins et al. 2015; Care Quality Commission 2020b; Furnish et al. 2020), yet the examination of the accuracy of timing of their administration is an area that has been unexplored in the care home setting. It is probable that this is a consequence of information not being routinely captured by paper-based records.

1.4.1.1 Parkinson's disease (PD)

Medicines used in the management of Parkinson's Disease (PD) are typically classed as time-sensitive with respect to their administration (Rehman 2010; Care Quality Commission 2020b). PD is a neurodegenerative condition presenting with a clinical picture of parkinsonism, a combination of motor symptoms including bradykinesia (slowness of movement), resting tremor and rigidity, as well as non-motor symptoms such as depression and anxiety; cognitive impairment; pain; constipation; and sleep disturbance (Ahlskog 2014; National Institute for Health and Care Excellence 2017b). PD is becoming more prevalent over time and current estimates suggest there are around 150,000 people living with PD in the UK (Doyle 2018; Brock et al. 2019). It is most common amongst older aged men (Parkinson's UK 2017, p. 13; Bloem et al. 2021). Most cases of PD are idiopathic, but in some cases there is a genetic component, particularly with onset of symptoms at a younger age (Bloem et al. 2021).

The symptomatic experience associated with PD varies between individuals and fluctuates over time (Parkinson's UK 2019), but is associated with functional impairment and reduced Quality of Life (QoL) (Parkinson's UK 2019; Bloem et al. 2021), as well as a decrease in life expectancy (Willis et al. 2012). There is currently no known treatment that can prevent, or reverse, the development of PD. As such, management focuses on symptom control, predominantly through the use of medicines (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). As the symptoms of PD are associated with a depletion of dopamine, a neurotransmitter involved in chemical signalling pathways in the basal ganglia, a part of the brain involved in regulating movement (Galvan and

Wichmann 2008), a core component in the management of PD is replacement of dopamine using dopaminergic medicines (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). However, careful dose titration is required to balance the control of PD symptoms against the development of adverse effects from these medicines, which include nausea; dyskinesias (involuntary movements); orthostatic hypotension; and impulse control disorders (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). Furthermore, symptom control can be affected by fluctuations in drug levels, for example due to dose omissions or delayed administration of medicines (Ahlskog 2014; Parkinson's UK 2019). This is particularly notable for levodopa, a dopaminergic medication that is typically used as first-line management of PD symptoms (Ahlskog 2014).

1.5 SCOPE OF THIS THESIS

As outlined above, whilst eMARs are becoming more common both in the UK and internationally, their implementation has focussed on addressing concerns such as safety and medicines waste in the care home sector (Al-Hamadani et al. 2015). In contrast, there has been limited research on their utility in examining medicines use in the care home population at scale in England. Therefore, the aim of this thesis is to consider the potential for the use of eMAR data in research and clinical practice relating to the long-term, older adult care home population in England. Specifically, Parkinson's disease (PD) will be used as a case study to undertake an exploratory and data-driven research design.

PD has been chosen as a case study due to the time-sensitive nature of medicines used in the management of this condition (Rehman 2010). This is notable, as one of the potential benefits of eMAR data is the ability to examine aspects of medicines use, including the timing at which medicines are administered, which cannot be readily studied using paper MAR charts alone. Traditionally, such research questions would require time- and resource-intensive methods such as observational studies. This may explain

why there is a paucity of studies examining dose omissions or the timing of medicines administration for PD medicines.

1.5.1 Thesis overview

This thesis undertakes secondary analysis of eMAR data, with a focus on medicines use in PD, using an exploratory and data-driven research design. Chapter Two examines the database provided for the secondary analysis presented in this thesis. It outlines potential data quality issues identified, and describes the pre-processing required, including the inclusion and exclusion criteria applied, to create a core study dataset on which subsequent analysis is based. Finally, it explores the representativeness of the core dataset to the older adult care home population for demographic factors of age and sex, and care home factors of geographical distribution and size.

Chapter Three uses dopaminergic medicines as a proxy for PD to identify this sub-population. Subsequently, an overview of the use of dopaminergic medicines is undertaken, examining the types of dopaminergic medicines prescribed, as well as the required frequency of administration and average daily levodopa equivalent dose (LED – a measure used to compare the dopamine requirements across different dopaminergic medicine regimens (Tomlinson et al. 2010)).

Chapters Four and Five examine administration patterns for dopaminergic medicines used in PD. In Chapter Four, the prevalence of, and reasons for dose omissions of dopaminergic medicines is explored. Meanwhile, Chapter Five assesses the timing of administration of levodopa doses, with both the traditionally used methodology (difference between time prescribed and time administered) and a novel approach to examine the difference between the observed and expected gap between administered doses. Finally, this thesis ends with a discussion on the potential benefits and limitations of harnessing the use of eMAR data both in academia and clinical practice, and recommendation steps to facilitate future use of this data source.

2 CORE DATASET CREATION

2.1 INTRODUCTION

As outlined in Chapter One, care homes, the majority of which are run by independent (i.e. for-profit and charitable) providers, support individuals (residents) of all ages with Activities of Daily Living (ADLs), with (nursing home) or without (residential home) the addition of nursing care, where this is needed for a variety of reasons (Competition & Markets Authority 2017). The size of care homes, measured by bed capacity, varies substantially (Care Quality Commission 2021a). Nursing homes are generally larger than residential homes, with an average capacity of 53 and 29 registered beds, respectively (Care Quality Commission 2021a). Extremely small homes (fewer than five registered beds) often provide very specialised services (Oscar Research [no date]).

Admissions to care homes may be short-term, for respite care or rehabilitation, or long-term, and may be self-funded or publicly funded (Competition & Markets Authority 2017). The most common reasons for requiring support varies by age, with mental health conditions and learning disability the most common reason in younger adults, and physical and cognitive impairments the most common in older adults (see Figure 1.1) (NHS Digital 2020). Individuals living in care homes are more likely to be older and female. Almost three-quarters of individuals living in care homes were reported to be female in the 2011 Census (Office for National Statistics 2013) and 82.5% were over the age of 65 years (Smith 2014).

2.1.1 Collection of study data

The secondary data used in this thesis was routinely collected through the routine use of an electronic medicines administration record (eMAR) system. There are numerous different types of eMAR systems on the market, with different approaches to, and degrees of digitisation of the medicines administration process. The eMAR system from which the data for this study was collected is a barcode-enabled system, which uses barcode technology to identify medicines; access medicine administration records; record administration attempts; and perform safety checks (ATLAS eMAR [no date]a). The system records the details of medicines, as well as other clinical items such as dressings and catheters. Information about the individual,

including demographic details, are recorded by staff within the care home. Meanwhile, most prescribed medicines are added by the dispensing pharmacy. These details are than updated in the records at the care home via synchronisation of the eMAR device with the system used at the dispensing pharmacy. However, medicines may also be added or updated by care home staff, for example where an acute change is required; for Over-the-Counter (OTC) medications (also known as homely remedies); or items that require dispensing from another pharmacy, which does not use the system.

Unique barcodes specific to the resident and medicine combination are added to medicine containers by the dispensing pharmacy. Medicines administration is mostly recorded by scanning the barcode of items using portable devices and following the on-screen instructions. This includes selecting the reason for non-administration where the attempt was unsuccessful. However, an override system exists to allow administration without the use of barcode-scanning, for example where a medicine has been supplied by a different dispensing pharmacy that does not offer the application of barcodes for this purpose as a service. Furthermore, paper records may be used for certain individuals or medicines as chosen by the care home or individual, or for a period of time if any technical or connectivity issues are encountered. Paper MAR charts may be printed from an online portal for this purpose. Training modules on the use of the device and safe medicines management are also available for staff administering medicines within the care home to complete.

There are care homes using this system across the UK (i.e. England, Scotland and Wales), providing care across a range of ages for various reasons (i.e. mental health conditions, learning disabilities, physical or cognitive impairment) and differing lengths of time (i.e. long-term or respite care). However, the majority of care homes using the eMAR system are based in England, with only 31 care homes with a Welsh or Scottish postcode area (7.87%) and the majority (95%) of individuals are recorded as being older adults (65 years of age or over).

2.2 AIM

The aim of this thesis is to consider the potential for the use of eMAR data in research and clinical practice relating to the long-term, English, older adult care home population, using Parkinson's disease as a case study. As the full database includes cases outside of these criteria, inclusion and exclusion criteria were applied to produce a core dataset restricted to older adults living in care homes in England, which forms the basis of further work presented in subsequent chapters of this thesis. Furthermore, as this thesis presents a secondary analysis of routinely collected data, an examination was made for possible data quality issues, with these addressed where possible.

Therefore, in summary, the aim of this chapter is to create a core dataset on which further work presented in the thesis will be based. This will include older adults living in care homes in England. In addition, the representativeness of the core dataset will be explored through comparison to national figures, obtained from Office for National Statistics (ONS) Census data (Office for National Statistics 2003,2013) and Care Quality Commission (CQC) (Care Quality Commission 2021a), for the following:

1. Geographical distribution of care homes
2. Care home size (bed capacity)
3. Age of residents
4. Sex of residents

2.3 METHODOLOGY

2.3.1 Data collection

Secondary data was used in this thesis, provided by Invatech Health Ltd. in pseudonymised form. Data was collected through routine use of the eMAR system. Barcodes identifying the medicine and patient it belongs to are added to original packs during the dispensing process at the local pharmacy. Synchronisation at the dispensing pharmacy and the care home allow data to be shared between the corresponding systems (ATLAS eMAR [no date]a). The barcodes on the original packs are scanned by staff at the care home during medicines management activities, for example booking in of stock and medicines administration using the eMAR device, which is approximately the size of a smartphone. Figure 2.1 shows a standard process for administering medicines using the barcode-enabled system.

Alerts may show at points during the process, for example if a wrong resident or wrong medicine is scanned, or if it is the wrong time for administering the medicine (ATLAS eMAR [no date]a). These should be actioned by staff when the pop-up is displayed. Alerts may be overridden by staff, but this decision is recorded by the system for audit purposes. Where a medicine is dispensed by a pharmacy that is not set up to produce barcodes used by the eMAR system, for example hospital issues, these may be administered by overriding the requirement for barcode scanning during the medicines administration process. Staff have unique logins to allow identification of who has been using the system within the medicines record. Operational reports are available to care home management to allow monitoring of how the system is being used by staff members (ATLAS eMAR [no date]a).

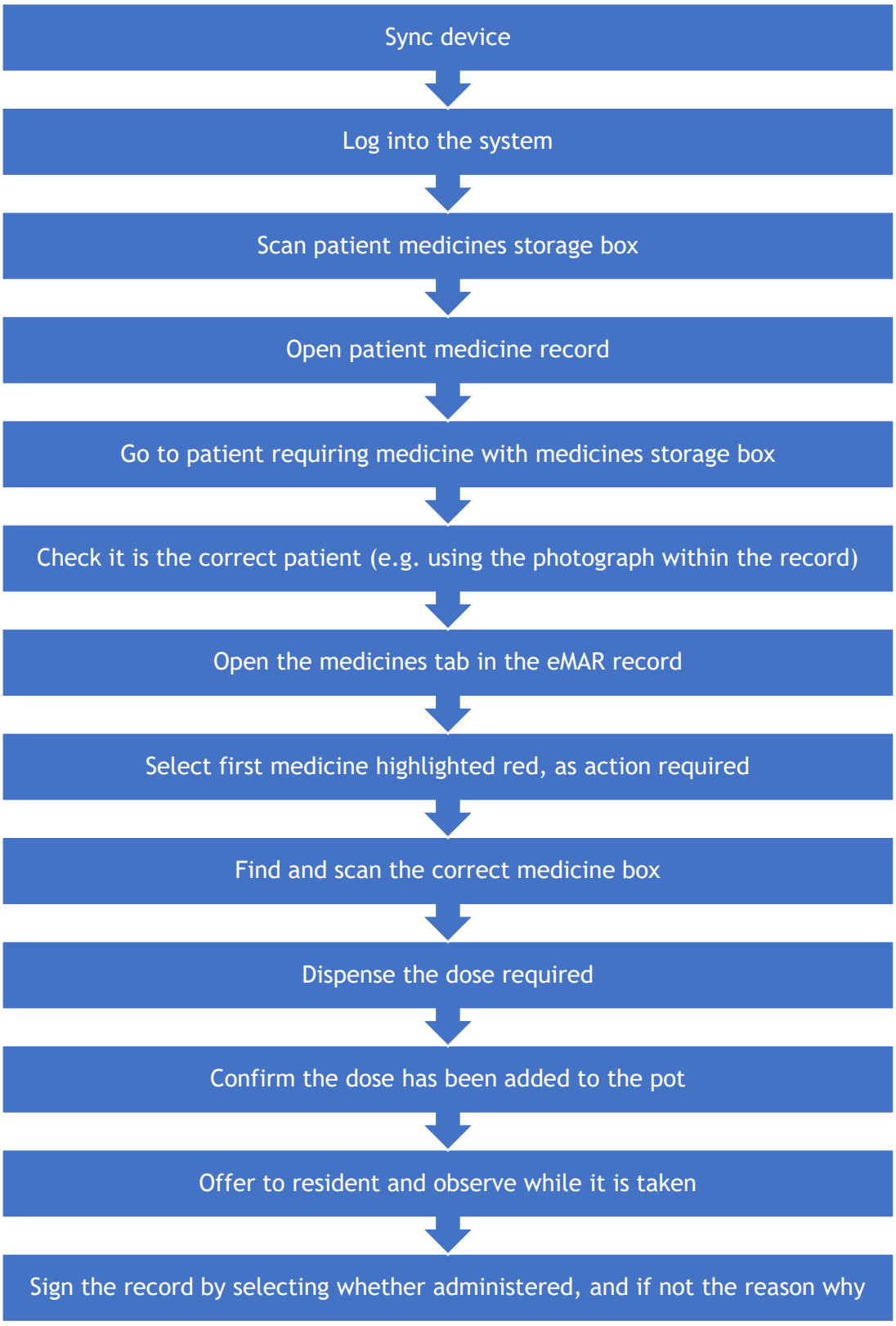

Figure 2.1: A standard process for administering medicines using the eMAR system (ATLAS eMAR [no date]a)

2.3.2 The database

Data was held in a SQL server 2016 database (Microsoft 2016) owned by Cardiff University on an encrypted, access-controlled server under a data sharing agreement between Cardiff University and Invatech Health Ltd. This was accessed remotely using unique login details via a Virtual Private Network (VPN) connection. Access to the pseudonymisation key was held by Invatech Health Ltd. alone, and no access to this was granted to Cardiff University. The data sharing agreement included further protections against re-identification of individuals, including password-protected access granted to a limited number of named individuals; and restrictions on combining with other individual-level data sources; and the requirement for review of work for potential re-identification risks prior to publication. As a result, ethical approval was not required for the secondary analysis presented in this thesis.

The database was set to be manually refreshed by the researcher using a stored procedure (a type of executable SQL code (Microsoft 2017b)) as required, which obtained data up to approximately midnight of that day through synchronisation with the eMAR providers' database. Where extracts were taken from the database by the researcher, these were held in Microsoft Excel 365 on OneDrive (Microsoft [no date]) and/or an encrypted hard drive.

2.3.2.1 Database tables

The database consisted of four tables containing data at resident; medicine; administration; and dispensing levels of detail. These tables included a range of fields, which are outlined in the Appendix 2, including several date-time fields, for which a default value of 01/01/1900 was used (Microsoft 2017a). The resident table was used for demographic details; the medicine table for details of active medicines (whether or not administered during the period); and the administration table for details on the timing and result of administration attempts. Dispensing data was not used as the process of medicines supply was outside of the scope of this thesis. Mandatory pseudonymised ID fields (denoting a resident, or resident-medicine combination) acted as primary keys, allowing linkage between tables.

It should be noted that the medicines table may also be used to record other items listed in the Dictionary of Medicines and Devices (dm+d) (NHS Business Service Authority [no date]) using the eMAR system, including devices (e.g. spacers and catheters). While these are included for the purpose of the creation of a core dataset for analysis of demographic factors presented in this chapter, consideration should be made for the removal of such items prior to any general assessment of medicines use within care homes in any future work. Where the term medicines is used in this thesis in relation to the core dataset, this refers to all dm+d items recorded by a care home using the eMAR device.

2.3.3 Creation of the core dataset

SQL code was used to create the core dataset. This was undertaken using SQL Server Management Studio (SSMS) 18 (Microsoft 2019), a tool which allows code to be used to retrieve data from a SQL database. The medicine table was used as the basis for this, joined to the resident table on the Resident ID using an inner join. This means that only matches where a resident was included in both the resident and medicine tables were included (W3 Schools [no date]). A new table was formed for the core dataset resulting from the application of the criteria outlined in this chapter to make the data static and improve system performance. This was produced by creating an empty table, into which data was inserted via a view (a piece of code that creates a virtual table, which is constructed only when needed and can be used to return data) (Microsoft 2017c).

Only individuals and medicines remaining active near the time of database refresh were included for analysis. This reduces the samples size considerably but was necessary to reduce the impact of challenges in identifying active individuals without access to a date when the resident was 'archived', as well as the challenges in identifying active medicines outlined in Table 2.1. These may occur where the recorded dates do not follow the expected sequence shown in Figure 2.2 or a medicine is re-started, with the previous medicine start and/or stop dates overridden.

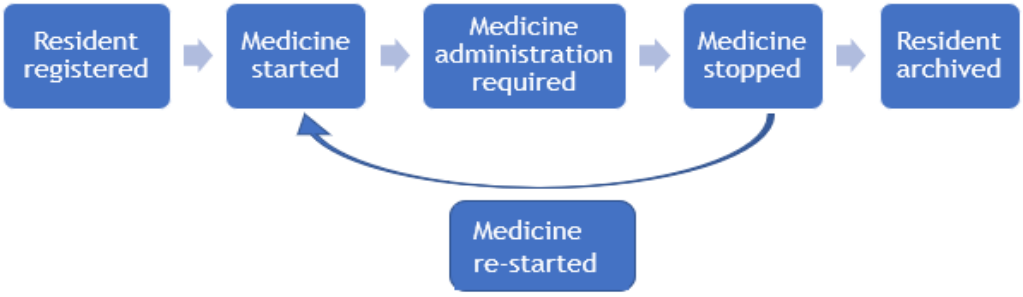

Figure 2.2: Expected sequence of events within date-time fields

The last database refresh was performed on the 20th of July 2020, obtaining data up to and including the 19th of July 2020. A 3-day period between the last day included in the study period and the last date included in the database refresh was used to reduce inaccuracies in the final days of the study period, which may occur due to delays in synchronisation of data at the care home, while still allowing the resident archive status and medicine status of 'Active' or 'Stopped' to be used with a fairly high degree of expected accuracy.

A 28-day period from 19th of June 2020 to the 16th of July 2020, inclusive, was examined. The period studied was standardised to 28 days across individuals to reflect the duration of a standard medicine cycle (Al-Hamadani 2018, p. 18). This also reduces intra-individual confounding being introduced as a result of changing medicine requirements and administration patterns, which may be seen over longer periods of time.

Table 2.1: Factors relating to data recording that pose challenges for identifying active medicines

Criteria	Frequency	Implication
Resident marked as archived but medicine remains active (medicine status is 'Active' and medicine stop date 01/01/1900 or after 19/07/2020)	122,490 medicines (20% of all medicines, 32% of medicines for individuals recorded as archived) across 12,380 individuals (33% of all individuals, 50% of those recorded as archived)	Use of medicines being active alone, without using archive status of individuals to identify whether still residing at the care home is likely to be inaccurate. Without a date of archival of resident, this makes study of individuals no longer residing at the care home difficult.
Medicine stop date is blank (dated 01/01/1900) but medicine status is 'Stopped'	6,865 medicines (1%) across 4,804 individuals (13%)	Unclear whether medicine is still in use as medicine stop date implies medication is still in use, but it is also marked as stopped.
Date medicine administration required after medicine stop date	275 medicines (<1%) across 246 individuals (1%) 86% of these medicines administered at least once after the date recorded as stopped, with a mean of 9 administrations over 6 days after the medicine stop date recorded.	Unclear whether medicine is still in use as medicine appears to be stopped but is still being recorded as required for administration. May represent medicines being re-started without update of the medicine stop date.
Medicine administration required recorded where medicine start date is blank (dated 01/01/1900)	21 medicines (<1%) across 20 individuals (<1%)	Possible data quality issue with recording or medicines due to be, but not yet, re-started.
Medicine start date after date medicine administration required	49,196 medicines (8%) across 12,490 individuals (34%) 80% of these medicines had at least one dose administered, with a mean of 46 administrations over 30 days.	Possible data quality issue with recording. 61% of these medicines also had a medicine stop date that was either blank (dated 01/01/1900) or after the medicine start date. Therefore, this may also represent medicines being re-started, with the new medicine start and stop dates overriding those previously recorded.
Medicine start date after medicine stop date (where medicine stop date not 01/01/1900)	7,133 medicines (1%) across 4,539 individuals (12%)	Possible data quality issue with recording, or medicines re-started without update of the medicine stop date. 20% of these medicines had a medicine start date after 2021, almost all of which had a medicine start date very far in the future (i.e. 2099, 2100). These may represent medicines that have never been started, for example where added in error.

2.3.3.1 Inclusion and exclusion criteria

The inclusion and exclusion criteria listed in Table 2.2 were applied during the creation of the core dataset. These are outlined in more detail in the following section.

Table 2.2: Inclusion and exclusion criterion applied in the creation of the core dataset

Criteria Type	Criteria Level	Criteria
Data availability	Resident	Resident ID recorded in both the medicine and resident tables
Registered individuals	Resident	Registered at least 28-days prior to the start of the study period
	Resident	Not recorded as archived
Demographics	Care home	English postcode area
	Resident	Aged between 65 and 105 years of age, inclusive
Active medicines	Medicine	Started before the 19/06/2020
	Medicine	Not stopped, or stopped after the 16/07/2020
Care home activity	Care home	At least 5 active older adult residents recorded
	Care home	Medicines required for administration daily throughout the study period

2.3.3.1.1 Registered individuals

Individuals were included where they were registered for at least 28 days prior to the start of the study period. This inclusion criteria was applied because both new resident status and short length of stay may act as confounders. For example, a short length of stay may indicate an individual had entered the home for respite care; had very limited life expectancy; or had greater care needs than the care home could manage.

Newly registered individuals may also be more prone to omissions, for instance due to regular medicines being recorded as required prior to the resident's arrival at the care home, or issues with obtaining the relevant medicine stock for new residents. In addition, medicines reconciliation should be performed for all individuals upon entering care (National Institute for Health and Care Excellence 2015b; Care Quality Commission 2020a). Therefore, the identification of specific subgroups for medicines review

may be considered to have more clinical utility in the settled care home population, as it is more likely that medicines may not have been reviewed for some time for these individuals.

Furthermore, delays in data entry onto the eMAR system for new residents may lead to inaccurate identification of medicines. When a new individual becomes a resident within a care home, the individual's details are inputted onto the system by the care home. Following this, the pharmacy input the details of medicines prescribed, and the care home enter any details of approved over-the-counter (OTC) medicines (also called homely remedies). Therefore, any data captured between these events could spuriously return incomplete details on medicines prescribed.

2.3.3.1.2 Demographics

Demographic inclusion and exclusion criteria were applied to identify older adults in English care homes. At the time of data extraction, there were care homes using the ATLAS system in England, Wales, and Scotland. However, most were based within England. Furthermore, adult social care is a devolved matter, with some national differences in policy between countries within the UK (Competition & Markets Authority 2017, p. 7). Therefore, care homes with a postcode area of 'A', 'BE', 'CF', 'G', 'LD', 'LL', 'PH', 'SA', 'TE', 'NP', blank or NULL, which may be based outside of England, were excluded.

As outlined in the introduction, differences in the most common reasons for requiring care support are seen between younger and older adults (see Figure 1.1) (NHS Digital 2020). This thesis focuses on medicines use in the older adult care home population, therefore individuals aged under 65 years were excluded from the analysis. Year of birth was used to approximate the age of individuals in the database by subtracting the Year of Birth from 2020. 650 individuals were excluded due to an age below 65 years. Meanwhile, 211 individuals aged over 105 years of age were excluded due to very low resident counts coupled with concerns over the potential for such extreme ages to be recording errors (e.g. failure to archive a resident). 203 (96.21%) of these individuals had an age of 120, which is likely to be a result of the Date of

Birth not being recorded on the eMAR device, resulting in the database recording a Year of Birth of 1900.

2.3.3.1.3 Active medicines

Medicines were included for analysis where these were active throughout the study period. As previously discussed, only medicines remaining active near the time of database refresh were included to reduce the challenges associated with identifying historical medicines use, as outlined in Table 2.1. Meanwhile, a specified period was studied to allow comparability between individuals and to capture recent patterns of medicine use.

2.3.3.1.4 Care home activity

Finally, care homes with either low numbers of active older adult residents or days in which no administration attempts were recorded at the care home were excluded. This included three care homes for which no administration attempts were recorded on either the first or the last day of the study period, suggesting that the care home may have either not yet started, or were no longer using, the eMAR device. All other care homes included had at least one administration attempt recorded every day throughout the 28-day period.

Exclusion of care homes with low levels of residency is an approach that has been used in previous research (Pont et al. 2018). As previously discussed, such care homes may represent very specialised services (Oscar Research [no date]), and therefore may be considered distinct from the broader care home population. Furthermore, where a care home has very few older adult residents, this may represent a care home that specialises in learning disability or mental health needs rather than the care of older adults. Low levels of active individuals may also be a result of either a newly registered or closing care homes.

2.3.4 Core dataset demographic analysis

Following the creation of the core dataset, an analysis of the representativeness of this, as compared to national datasets, was undertaken for age, sex, care home size and care home geographical distribution. Data from the CQC Directory from January 2021 was used as the

basis for comparison of expected to actual geographical distribution of care homes and registered beds across England (Care Quality Commission 2021a). This directory contains details of all regulated services across health and social care within England. Therefore, it was filtered to only include care homes providing adult social care services. More details of the approach used for this can be found in the Appendix 3. Meanwhile, details on the age and sex distribution of the older adult care home population in England was obtained from 2001 and 2011 Census data (Office for National Statistics 2003,2013). Further details of how the Census data was obtained from the Office for National Statistics (ONS) via the Nomis browser are found in Appendix 4. Age was categorised into 65 to 74 years; 75 to 84 years; and 85 years and over[3], while sex was categorised into male and female. Both the CQC Directory and ONS Census data were used under the Open Government Licence for public sector information (The National Archives 2021).

As detailed previously, the ages of residents in the core dataset were calculated by subtracting the Year of Birth from 2020. Meanwhile, sex was derived using the recorded Title as a proxy to produce three categories; male, female and unknown (where Title could not reasonably be used as a proxy e.g. a Title of Doctor). Data on the count of individuals by age; the count of individuals by sex; the count of individuals and count of care homes by postcode area; and the count of individuals by care home were extracted using SQL code. A combination of Microsoft Excel 365 (Microsoft [no date]) and R v3.6.1 (R Core Team 2019), run in RStudio v1.4.1717 (RStudio 2021), were used for statistical analysis and creation of figures.

[3] In the 2001, four age categories were presented (65 to 74 years; 75 to 84 years; 85 to 89 years; and 90 years and over). However, the latter two categories were aggregated to allow comparison with the 2011 Census
Office for National Statistics. 2013. *Communal establishment management and type by sex by age*. Office for National Statistics. Available at: https://www.nomisweb.co.uk/census/2011/dc4210ewla [Accessed: 06/02/2021]. , for which these were presented as a single category. Census Office for National Statistics. 2003. *Type of communal establishment and sex by resident type and age*. Office for National Statistics. Available at: https://www.nomisweb.co.uk/census/2001/st126 [Accessed: 06/02/2021].

2.3.4.1 Geographical distribution of care homes

The geographical distribution of care homes in the core dataset compared to the CQC Directory (Care Quality Commission 2021a) was conducted at postcode area level. Estimations of the proportion of care homes and registered beds included in the core dataset were calculated by dividing the number of care homes in the core dataset by the number of care homes in the CQC Directory; and dividing the number of individuals in the core dataset by the number of registered beds in the CQC Directory, respectively. The distribution of these was visualised in Microsoft Excel 365 (Microsoft [no date]), to examine the distribution and identify the presence of any outlying postcode areas with over- or under-representation in the core dataset.

Two scattergraphs were plotted to visualise the correlation between the number of care homes in the core dataset and the CQC Directory; and the number of individuals in the core dataset to the number of registered beds in the CQC Directory, respectively. A Q-Q plot was created using R v3.6.1 (RStudio 2021; R Core Team 2019) for each of these to examine their distribution. Where Q-Q plots were suggestive of a non-normal distribution, Spearman's Rho was used to assess for a statistically significant correlation between the geographical distributions seen in the core dataset and the CQC Directory for the number of care homes and the number of individuals/registered beds, respectively (RStudio 2021; R Core Team 2019).

2.3.4.2 Care home size

An analysis of the average number of residents per care home in the core dataset compared to the average number of registered beds in the CQC Directory (Care Quality Commission 2021a) was also undertaken. Microsoft Excel 365 (Microsoft [no date]) was used for visualisation and Q-Q plots, created using R v3.6.1 (RStudio 2021; R Core Team 2019) were plotted to assess for a normal distribution. As a considerable right skew was seen in the number of registered beds per care home recorded in the CQC Directory data, Wilcoxon Sum Rank test was used to test for a statistically significant difference in distribution between the numbers of residents per care home in the core dataset compared to the number of registered beds in the CQC Directory (RStudio 2021; R Core Team 2019; Care Quality Commission 2021a).

2.3.4.3 Age

The ages in the core dataset were grouped in Microsoft Excel 365 (Microsoft [no date]) into three categories of ages 65 to 74 years; 75 to 84 years; and 85 years and over to allow comparison to 2001 and 2011 Census data (Office for National Statistics 2003,2013). The distribution was visualised using Microsoft Excel 365 (Microsoft [no date]). Finally, Pearson's chi-squared test for independence was performed using R v3.6.1 (RStudio 2021; R Core Team 2019) to assess for a statistically significant difference in the distribution across the three datasets.

2.3.4.4 Sex

As previously outlined, the Title field within the database was used as a proxy to classify the sex of residents in the core dataset as male, female, or unknown. The majority of individuals (99.76%) could be classified as either male or female in this way. The results were visualised in Microsoft Excel 365 (Microsoft [no date]), and a Pearson's chi-squared test for independence was undertaken using R v3.6.1 (RStudio 2021; R Core Team 2019) to assess for a statistically significant difference across the three datasets.

2.4 RESULTS

2.4.1 Creation of the core dataset

Table 2.3 outlines the result of the application of inclusion and exclusion criteria during the formation of the core dataset. Following the application of all inclusion and exclusion criteria, 77,646 (12.98%) medicines, 9,082 (24.38%) residents and 310 (78.68%) care homes remained. The majority of exclusions of residents and medicines were a result of the resident being recorded as archived, accounting for 86.25% and 73.45% of the total exclusions, respectively. Meanwhile, the most common reason for care home exclusion was the result of the postcode area recorded (45.24%).

Table 2.3: The result of application of inclusion and exclusion criteria during the creation of the core dataset, in order of execution.

Exclusions			Care Homes			Residents			Medicines		
Order Applied	Level	Reason	Total	% of Total	% of Total Exclusions	Total	% of Total	% of Total Exclusions	Total	% of Total	% of Total Exclusions
		Total	394	100.00	0.00	37258	100.00	0.00	598275	100.00	0.00
1	Resident	No individual-level details recorded	390	98.98	4.76	37240	99.95	0.06	598198	99.99	0.01
2	Resident	Resident registered less than 28 days prior to the study start date	381	96.70	10.71	35494	95.27	6.20	581323	97.17	3.24
3	Resident	Resident archived	381	96.70	0.00	11193	30.04	86.25	198929	33.25	73.45
4	Care home	Not an English postcode area	343	87.06	45.24	10226	27.45	3.43	178680	29.87	3.89
5	Resident	Not between 65 and 105 years of age, inclusive	329	83.50	16.67	9350	25.10	3.11	165738	27.70	2.49
6	Medicine	Medicine not started prior to start of study period	328	83.25	1.19	9301	24.96	0.17	141668	23.68	4.62
7	Medicine	Medicine stopped prior to end of study period	328	83.25	0.00	9165	24.60	0.48	78167	13.07	12.20
8	Care home	Less than 5 individuals in home meeting above criteria	313	79.44	17.86	9129	24.50	0.13	77907	13.02	0.05
9	Care home	No medicines scheduled for administration at the care home on the first or last day of study period	310	78.68	3.57	9082	24.38	0.17	77646	12.98	0.05

2.4.2 Core dataset demographic analysis

2.4.2.1 Geographical distribution

78 of the 100 postcode areas in the CQC Directory (Care Quality Commission 2021a) had one or more care home(s) in the core dataset, with a mean of 2.81% of care homes and 2.13% of registered beds in England represented (Figure 2.3). However, this was skewed by outlier postcode areas with a high prevalence of care homes and registered beds represented in the core dataset, with maximum values of 16.28% and 12.16%, respectively. Q-Q plots showed a right skew, although more so for the core dataset (Figures 2.4 and 2.5). Therefore, Spearman's Rho was used to assess for a statistically significant correlation between the distributions found in the core dataset and the CQC Directory. This found a statistically significant moderate correlation for both number of care homes and number of individuals/registered beds (0.487 and 0.421, respectively; $P<0.001$). Despite this, a considerable amount of dispersion is seen, as shown in Figures 2.6 and 2.7.

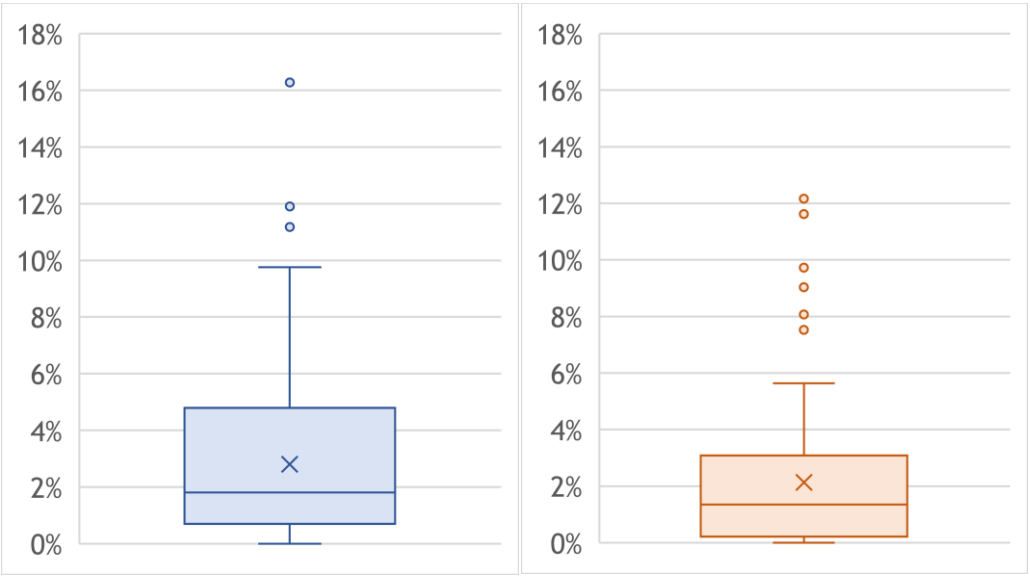

Figure 2.3: Number of care homes (left) and residents (right) in the core dataset by postcode area, as a percentage (%) of the care homes (left) and registered beds (right) in the CQC Directory (Care Quality Commission 2021a)

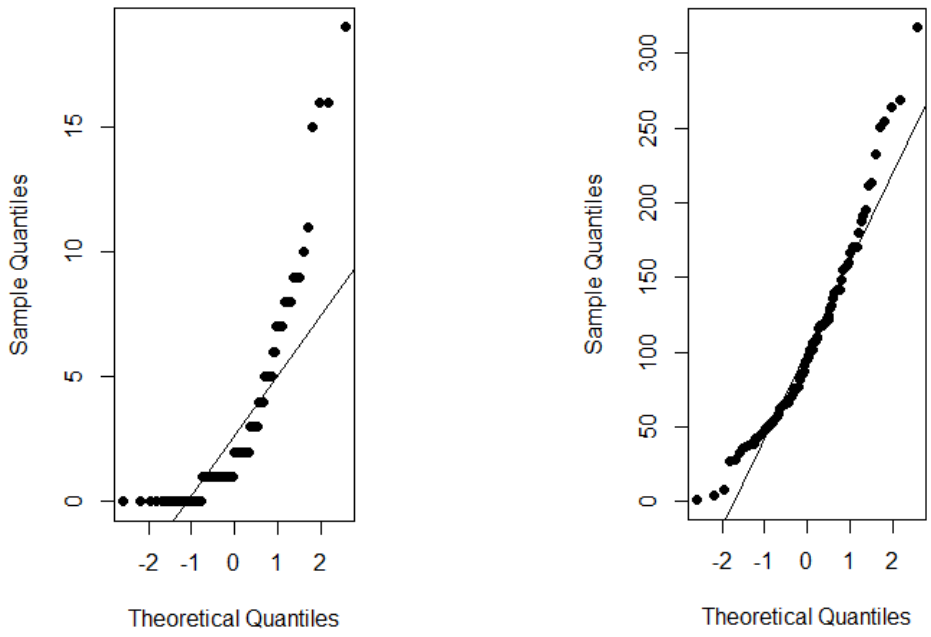

Figure 2.4: Q-Q plots demonstrating the distribution of the number of care homes per postcode area in the core dataset (left) and the CQC Directory (right) (Care Quality Commission 2021a)

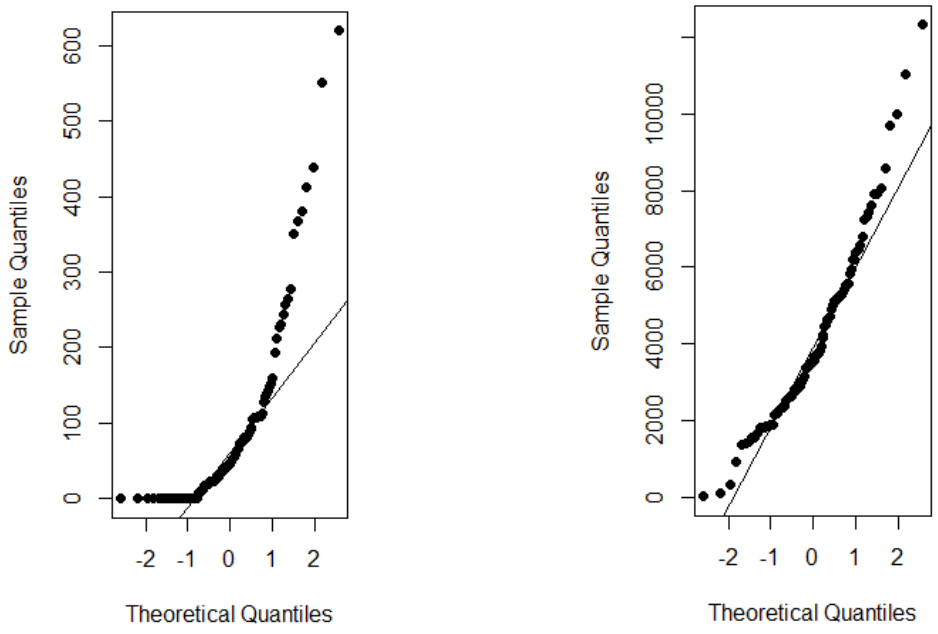

Figure 2.5: Q-Q plots demonstrating the distribution of the number of residents (left) and registered beds (right) per postcode area in the core dataset (left) and the CQC Directory (right) (Care Quality Commission 2021a)

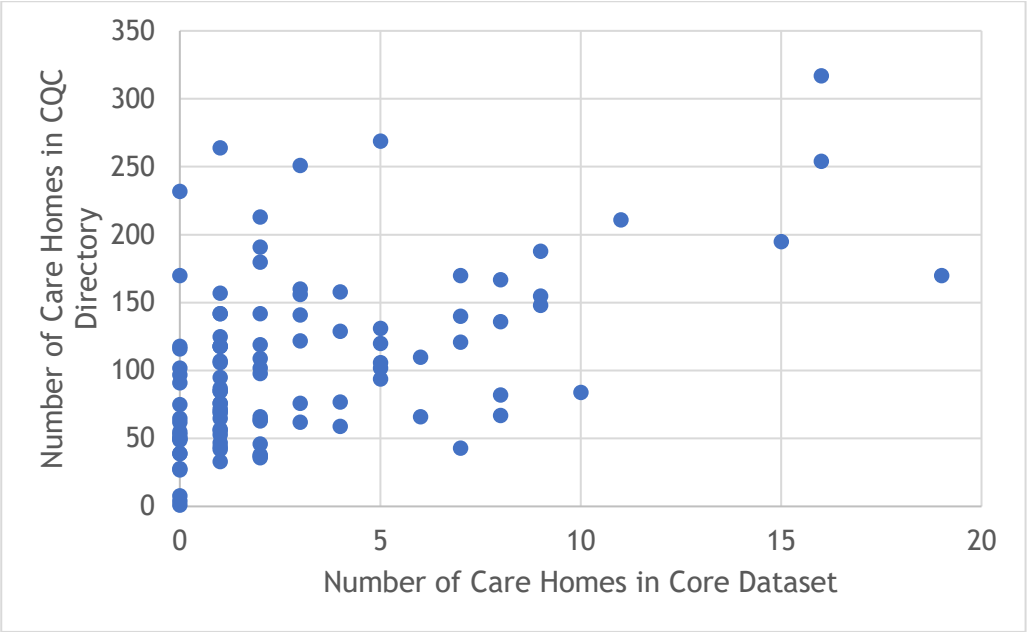

Figure 2.6: Scattergraph showing the association between the number of care homes per postcode area in the core dataset and CQC Directory (Care Quality Commission 2021a)

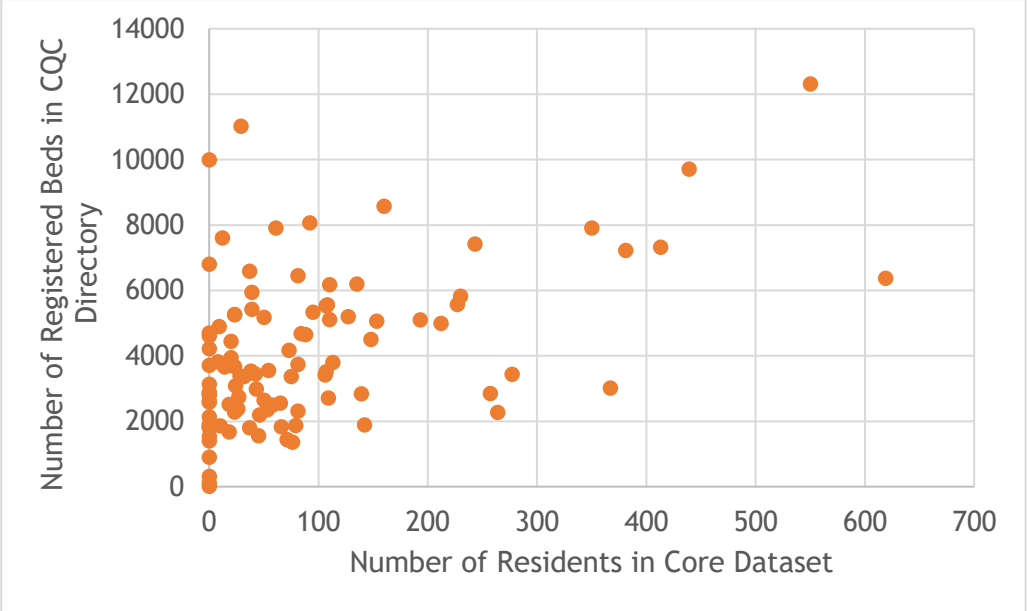

Figure 2.7: Scattergraph showing the association between the number of residents/registered beds per postcode area in the core dataset and CQC Directory (Care Quality Commission 2021a)

2.4.2.2 Care home size

On average, the number of individuals per home in the core dataset was lower compared to the number of registered beds per home in the CQC Directory (Care Quality Commission 2021a), with medians of 27 and 35, respectively. Furthermore, as demonstrated in Figure 2.8, a greater number of outliers were seen within the CQC Directory. Therefore, while the number of individuals per home in the core dataset showed an approximately normal distribution, a considerable right skew was seen in the CQC directory (Figure 2.9). The difference in distribution was found to be statistically significant ($P<0.001$).

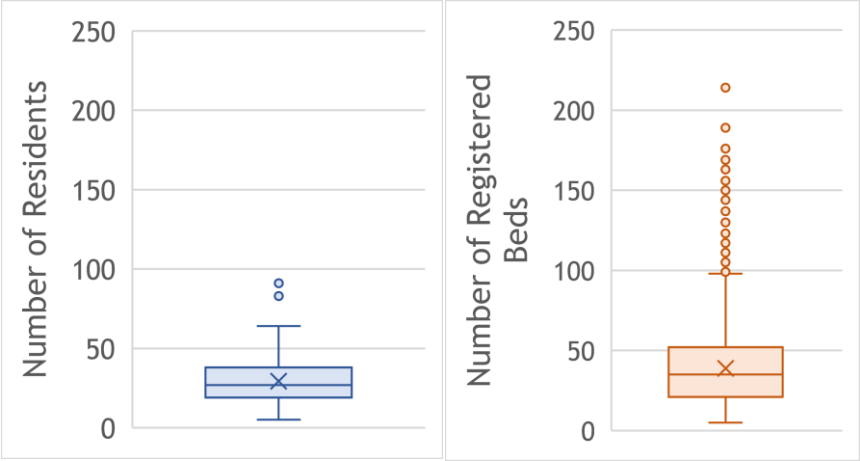

Figure 2.8: Number of residents (left) and registered beds (right) per care home in the core dataset (left) and the CQC Directory (right) (Care Quality Commission 2021a)

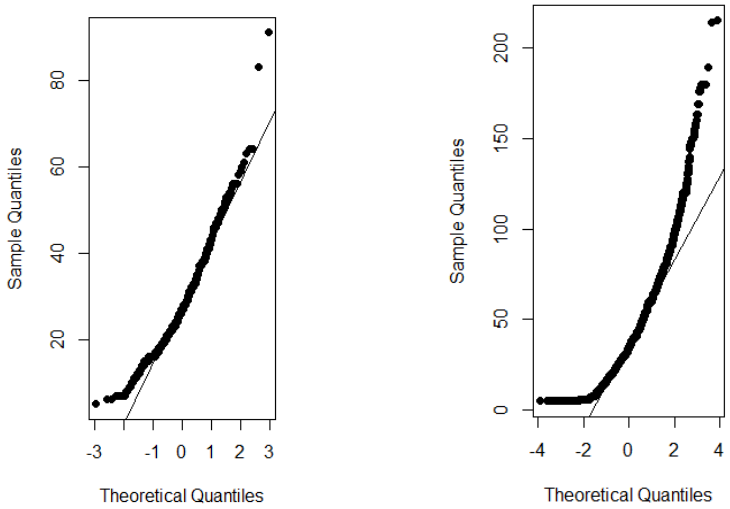

Figure 2.9: Q-Q plots demonstrating the distribution of the number of residents (left) and registered beds (right) per care home in the core dataset (left) and the CQC Directory (right) (Care Quality Commission 2021a)

2.4.3 Age

The distribution of the ages of individuals in the core dataset showed an approximately normal distribution, with a mean age of 85.82 (95% confidence interval 85.76 - 85.88), a median age of 87 and an interquartile range of 81 to 92 years of age. An increasing proportion of individuals aged 85 years and over was seen from the 2001 Census (Office for National Statistics 2003) to the core dataset (extracted in 2020), alongside a decreasing proportion of individuals aged 75 to 84, with little change for those aged 65 to 74 years (Figure 2.10). Pearson Chi Squared test found this variation in the distribution of ages of individuals to be statistically significant (P<0.001).

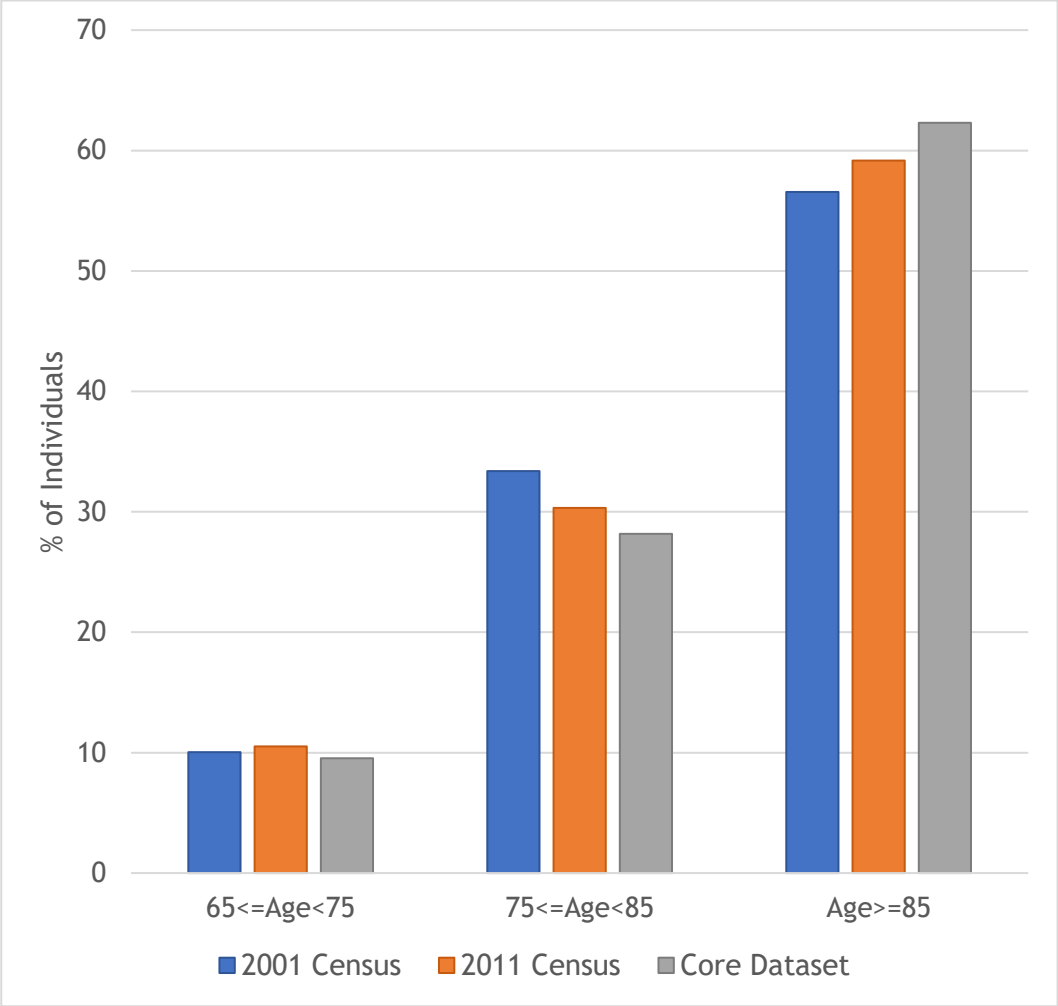

Figure 2.10: Clustered bar chart showing the percentage (%) of individuals by age category in the 2001 Census (Office for National Statistics 2003), the 2011 Census (Office for National Statistics 2013), and the core dataset

2.4.4 Sex

For sex, a trend towards an increasing male proportion within the care home population was found, with 29% male in the core dataset (extracted 2020), compared to 26% in the 2011 Census (Office for National Statistics 2013) and 23% in the 2001 Census (Office for National Statistics 2003) (Figure 2.11). Pearson's Chi Squared test found this difference to be statistically significant ($P<0.001$).

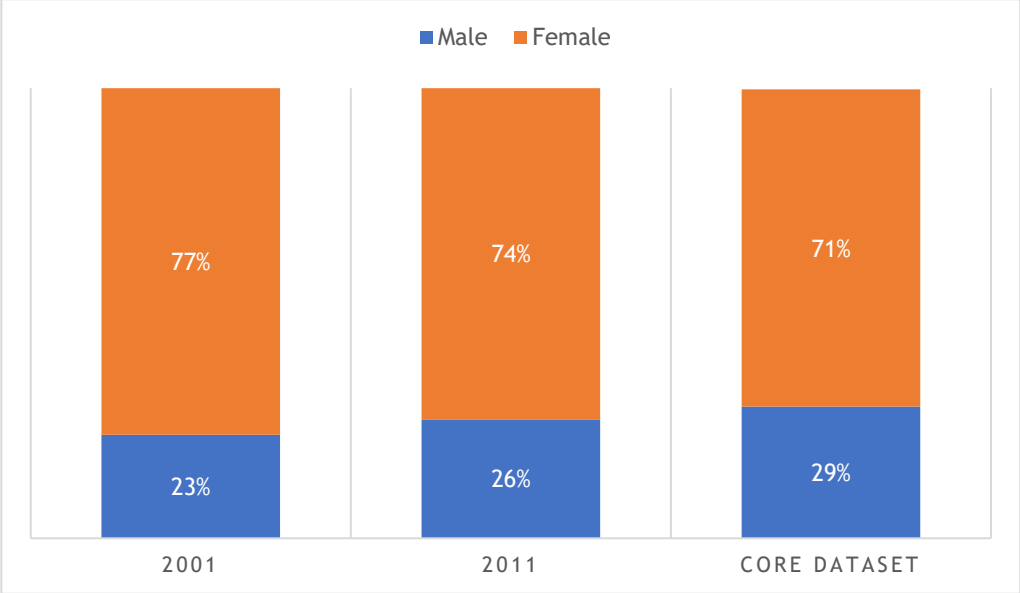

Figure 2.11: Stacked bar chart showing the percentage (%) of individuals by sex in the 2001 Census (Office for National Statistics 2003), the 2011 Census (Office for National Statistics 2013), and the core dataset[5]

2.5 Discussion

In view of the results presented in the previous section, the core dataset can be considered moderately representative of the care home population for the factors examined, with the exception of care home size. However, not all possible confounding factors have been explored in this analysis. For example, resident ethnicity, type of home (i.e. residential or nursing), and CQC inspection ratings could not be assessed. Furthermore, the deployment of an eMAR system is likely to act as a confounder itself. As such, no results of this study should be taken to confer any generalisability across the older adult care home population of England.

[5] Title was used as a proxy for sex in the core dataset. See 2.3.3.4 Sex for more details.

2.5.1 Data exclusions

A large proportion of residents and medicines within the database were excluded during the creation of the core dataset. The majority of these exclusions were a result of the individual being recorded as 'archived' (see Table 2.3 for more details). As the eMAR system from which the data presented in this thesis was collected has been in use within care homes for several years and estimates of the average length a stay in English care homes are around 1-2 years (Forder and Fernandez 2011, pp. 9-12; Lievesley et al. 2011, pp. 23-25; Steventon and Roberts 2012), this can be considered expected. The absence of a date of resident archival therefore acts as a significant limitation, as this causes challenges not only for examining historic medicines use, but also reduces the sample size achievable through this data source. Individuals with no items recorded as active throughout the study period were also excluded. However, examining the data on the exclusions (Table 2.3), this impacted a minority of records, with only one care home and 185 individuals excluded for this reason.

2.5.2 Core dataset demographics

2.5.2.1 Geographical distribution

Although a low proportion of all care homes in England was represented, the core dataset still represents a larger population of care home residents than many previous UK studies in this field (Barber et al. 2009; Jokanovic et al. 2015; Al-Hamadani 2018) and the use of the eMAR system provides reassurance that the individual was indeed a care home resident. This is difficult to establish from primary care data. Therefore, approaches often use rigorous inclusion criteria to reduce the risk of accidental inclusion of community-dwelling individuals. However, these may exclude around a third of care home residents (Shah et al. 2010; Shah et al. 2012).

A lower number of residents in the core dataset were found to be represented as a proportion of registered beds in the CQC Directory (Care Quality Commission 2021a) compared to the proportion of care homes represented (medians of 1.35% and 1.81%, respectively; see Figure 2.3 for more detail). However, this can be considered expected, as it is unlikely that care homes would have 100% occupancy of registered beds. This is

demonstrated by Knight Frank's UK Care Home Trading Review 2019, which reported occupancy rates of around 90% in the financial year of 2018/19 (Brame et al. 2019). Furthermore, a small proportion of individuals within the home may be excluded from the core dataset for other reasons, for example due to age exclusions applied.

Despite a number of postcode areas not being represented within the study dataset, a moderate correlation was found with the distribution seen in the CQC Directory (Care Quality Commission 2021a) (see section 2.4.2.1 'Geographical distribution' for more detail). However, a limitation of the analysis of geographical distributions is the difference in dates of extraction of the CQC Directory data and the core dataset. This may impact upon results, as there may have been changes in the number of homes and beds registered with the CQC across England in the six-month interlude between database refresh and the CQC Directory used. Despite this, it can be hypothesised that, although changes within this period are likely to have been seen, this would have impacted a small number of homes and, as such, the overall effect on the proportions represented in the core data presented in this chapter would be insignificant.

2.5.2.2 Care home size

A significantly lower residency level was seen in the care homes in the study dataset compared to the numbers of registered beds in the CQC Directory (Care Quality Commission 2021a) (see section 2.3.3.2 'Care home size' for more detail). This is notable, as it is feasible that this may act as a confounder. Very little previous work examining the association between care home size and medicines use could be found, with those identified including a systematic review of polypharmacy, which found a negative association with care home size (Jokanovic et al. 2015), and a study of psychotropic prescribing, which found no association with care home size (Westbury et al. 2018). Meanwhile, a study of nutritional care found smaller care homes were more likely to deliver person-centred care but were less likely to meet regulations such as the completion of audits and surveys (Burger et al. 2017).

However, as discussed previously, it should be recognised that the number of individuals per care home in the core dataset is likely to be an underestimation of the care homes total registered beds due to exclusion criteria applied in the creation of the core dataset (e.g. for age and active medicines use), alongside a proportion of registered beds likely to be unfilled (estimated to be around 10% in previous research (Brame et al. 2019)). Despite this, a statistically significant difference in distribution remained when the number of registered beds is adjusted to 90% of the total, to the nearest whole number (medians 27 vs 32, $P<0.001$). Nevertheless, further research is needed verify this disparity seen, alongside examining the effect of care home size on medicines use, particularly in relation to administration patterns. This should ideally be examined alongside the number of staff administering medicines within the care home in adjusted modelling, as it is probable that there is a degree of interconnection between these two variables.

2.5.2.3 Age

A continuation of the trend in change in age distribution between the 2001 Census (Office for National Statistics 2003) and 2011 Census (Office for National Statistics 2013) was also seen between the 2011 Census and the core dataset (2020), with an increase in individuals aged 85 years and over (Figure 2.10). Possible explanations for this could be either older age at admission, increased length of stay, or a combination of both. Given that a decrease was seen for the age category 75-84 years, it may be hypothesised that an increase in age at admission is the dominant cause, linked with improvements in the health of the general population (Smith 2014). Data from the Scottish annual Care Home Census supports this, showing as slight increase in age at admission between 2009 and 2019 (median 81 to 82 years; mean 76 to 78 years), alongside a slight decrease in the number of long-stay residents aged 65 years and over (32,226 to 30,914, -4%) (Public Health Scotland 2020b,a).

2.5.2.4 Sex

As with age, a continuation of the trend towards an increase in the proportion of male residents and a decrease in the proportion of female residents was seen between the 2011 Census (Office for National Statistics 2013) and the core dataset (2020) (Figure 2.11). However, it should be noted that a limitation of this study is the use of 'Title' as a proxy for sex which may not accurately categorise individuals in all cases, for example where an individual's gender identity does not reflect their biological sex. Furthermore, for a minority of individuals, it was not possible to use Title as a proxy, for example where this was not recorded or a Title such as Doctor was used.

2.5.3 General limitations and considerations for future work

As previously mentioned, the representativeness of the core dataset could not be explored for certain factors, including resident ethnicity, care home type (i.e. nursing or residential) and CQC inspection rating. Ethnicity, in particular, is a factor that is often overlooked, but may be increasingly important for inclusion in studies given recent evidence that both ethnicity and polypharmacy are associated with the risk of a positive COVID-19 test result (McQueenie et al. 2020). As this study was conducted in the UK during the period in which policy was for testing only individuals in the hospital setting, it is expected that the majority of individuals would have had significant signs and symptoms, and so a positive test result in these circumstances may also denote severity of illness (McQueenie et al. 2020). As a result, further research is needed to explore the representativeness of the core dataset for such factors, and inclusion of these should be considered in any future research examining the use of medicines within care homes with adjusted modelling.

Several notable characteristics of the study database were identified, which should be taken into consideration in future work using this data source. Firstly, despite the majority of care homes in the database recorded as having an English postcode area, the core dataset only represented around 2-3% of all care homes in England. Therefore, very granular analyses or use of the database to examine other UK countries may result in failure to

achieve adequate statistical power. Secondly, as noted in the methodology section 2.3.1.1 'Database tables', the medicine table of the database contained devices listed in the dm+d alongside medicines. Therefore, future work aiming to examine medicines use in general in the care home population should include steps to exclude such devices. Thirdly, while reducing the risk of data not being up-to-date due to delays in data synchronisation at the care home, the use of a 3-day period between the final day of the study period and the date of database refresh resulted in 52 items being included in the core dataset where these were recorded as having been stopped between the 17th of July 2020 and the 20th of July 2020. Although this represent a very small proportion of the core dataset (0.07%), exclusion of such cases in future work should be considered where the aim is to identify medicines for review by health professionals.

Some desirable fields were not available in the database, posing challenges for analysis. For example, the absence of an archive date field, alongside a significant number of archived individuals where medicines were not recorded as stopped either via the Medicine Stop Date or the Medicine Status (Table 2.1) meant that an individual having no active medicines could not be robustly used as a proxy for continued presence at the care home. As a result, this limits the ability to use this data source to examine historical medicines use. Discussion with the eMAR provider should be considered to explore the possibility of adding such fields where this data source is used in future work. Finally, although the use of eMAR has been found to reduce the rate of recording errors seen in paper MAR charts (Al-Hamadani et al. 2015), some possible data quality issues were identified in the database. For example, there was evidence suggesting missing data in some fields, such as Year of Birth. Approaches for remedying this should be considered, including the possibility of a 'eMAR record completeness' dashboard for use by the care home to check that all data fields are completed.

2.6 CONCLUSION

Through the application of inclusion and exclusion criteria described in this chapter, a core dataset has been created for older adult, English care home residents, for which the eMAR system was used throughout the 28-day study period. This will form the basis of the analyses conducted in subsequent chapters of this thesis. This appears to show a fair degree of representativeness with the larger older adult care home population of England for variables of geographical distribution, and age and sex of individuals. However, several limitations of the data source were identified, including absence of desirable data fields, and evidence suggesting missing data in some fields.

3 PARKINSON'S DISEASE

3.1 INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative condition associated with a deficiency in dopamine activity (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b; Bloem et al. 2021). Individuals with PD experience motor symptoms of bradykinesia (slowness of movement), resting tremor and rigidity, alongside non-motor symptoms such as depression and anxiety; cognitive impairment; pain; constipation; and sleep disturbance (Bloem et al. 2021). As there is currently no cure, management of PD focuses on symptom control, predominantly using dopaminergic medicines as shown in Figure 3.1 (i.e. dopamine agonists, Monoamine Oxidase-B Inhibitors, catecholamine-O-methyltransferase inhibitors and levodopa) alongside other agents for managing non-motor symptoms (e.g. medicines for managing dementia symptoms, laxatives) (British National Formulary [no date]a; Ahlskog 2014; National Institute for Health and Care Excellence 2017b; Tidy and Bonsall 2018; Bloem et al. 2021). Careful monitoring for, and management of, adverse effects of dopaminergic therapy, including dyskinesias (uncontrolled, involuntary movements), psychotic symptoms, and impulse control disorders, is also needed (British National Formulary [no date]a).

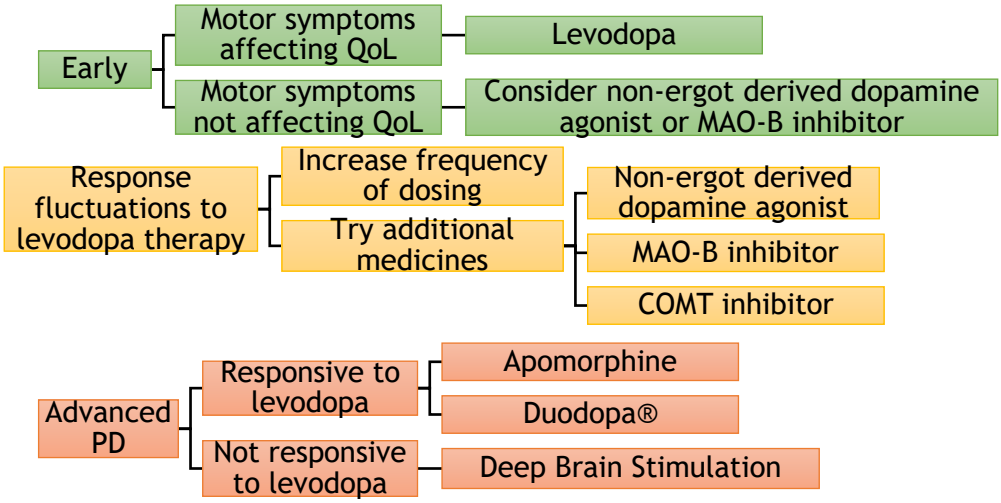

Figure 3.1: Summary of National Institute for Health and Care Excellence (National Institute for Health and Care Excellence 2017b) and British National Formulary (British National Formulary [no date]a) guidance on management of PD using dopaminergic medicines. (PD – Parkinson's Disease; QoL – Quality of Life; MAO-B – Monoamine Oxidase Type B; COMT inhibitor – Catechol-O-Methyltransferase).

3.1.1 Dopaminergic medicines

3.1.1.1 Levodopa

As dopamine itself cannot pass the blood-brain barrier, it is administered in the form of levodopa, a precursor to dopamine (Ahlskog 2014). Levodopa is preferred as first-line therapy for the management of PD where motor symptoms are causing the individual disability or reduced quality of life (Figure 3.1) (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). It is administered alongside a decarboxylase inhibitor to reduce the peripheral conversion of levodopa to dopamine (Ahlskog 2014). This allows a greater proportion of the dose to act on neuroreceptors beyond the blood-brain barrier, reducing the levodopa dose needed for clinical effectiveness and reducing the adverse effects that occur as a result of activation of peripheral dopamine receptors (e.g. gastrointestinal and cardiovascular disturbances) (British National Formulary [no date]a; Carvey 2010; Ahlskog 2014; National Institute for Health and Care Excellence 2017b; Tidy and Bonsall 2018). In the UK, the levodopa-decarboxylase inhibitor combinations used are co-careldopa (carbidopa and levodopa) and co-beneldopa (benserazide and levodopa) (British National Formulary [no date]a).

Over time, individuals with PD will often experience a shortening of the clinically effective period of levodopa, and an increased incidence of adverse effects such as dyskinesias (Ahlskog 2014). This is thought to be a result of progressive loss of dopamine neurons (Ahlskog 2014). One approach for managing such short-duration responses to levodopa is dose fractionation, the introduction of more frequent dosing to improve the management of symptoms (Ahlskog 2014; Nyholm and Stepien 2014). Surprisingly, there is a paucity of research examining the frequency of levodopa administration and, notably, no studies exploring dosing frequency in the care home setting could be found.

The most detailed study exploring dose fractionation that was identified examined this (defined as more than 4 daily doses) in individuals visiting a Swedish neurology clinic who had been taking levodopa for at least four years (Nyholm and Stepien 2014). This reported that the majority (85%) of

individuals received multiple daily doses (Nyholm and Stepien 2014). The number of daily doses was observed to increase over time, with a median of 4-6 daily doses between 4 and 13 years after starting levodopa, rising to 8 doses at 16 years (Nyholm and Stepien 2014). However, lower rates of fractionation were seen in older individuals, and an increasing variability in the frequency of dosing was seen as time since levodopa initiation increased (Nyholm and Stepien 2014).

Similar results have been reported in other studies. For example, an examination of adherence to PD medicines in the community setting reported an average of around 4 administration episodes per day, with lower adherence seen where a greater number of administrations were required per day (Grosset et al. 2009). Meanwhile, several small sample size studies conducted in the late 1900s have examined dosing fractionation as part of the analysis of the efficacy of new therapeutic management for PD. This includes Sinemet® (Hutton et al. 1988; Hutton and Morris 1991), and selegiline (Sivertsen et al. 1989), with around 4-6 doses of levodopa administered per day reported.

Finally, a large French retrospective study of levodopa regimens before and after the commencement of entacapone found 30% of individuals received more than 4 daily doses of levodopa at baseline (Damier et al. 2008). This suggests a lower rate of dose fractionation, despite over one-third of these being 5-10 years post-PD diagnosis, and around a quarter over 10 years (Damier et al. 2008). However, this study did not report the average number of daily doses across participants and did not provide sufficient details within the results to allow for calculation a mean or median. From the results provided, it is possible the median was 4 (Damier et al. 2008). Furthermore, as different inclusion criteria were applied across studies, this makes the results difficult to compare (Damier et al. 2008) (Nyholm and Stepien 2014) (Grosset et al. 2009) (Hutton et al. 1988; Hutton and Morris 1991) (Sivertsen et al. 1989).

3.1.1.2 Dopamine agonists

There are two broad categories of dopamine agonists: ergot-derived and non-ergot derived. Although both have been shown to be clinically effective in the management of motor symptoms experienced in PD, non-ergot derived dopamine agonists are preferred. This is because ergot-derived dopamine agonists such as cabergoline can result in rare fibrotic reactions including pleural and cardiac valve thickening that compromise pulmonary and cardiac functioning (British National Formulary [no date]a; LeWitt 2010; Tidy and Bonsall 2018; Luo et al. 2020). Non-ergot derived dopamine agonists include the oral agents pramipexole and ropinirole, along with the transdermal agent rotigotine (British National Formulary [no date]a; Luo et al. 2020). Levodopa is generally preferred over dopamine agonists as it is associated with a greater improvement in motor symptoms, with a lower risk of developing adverse effects such as orthostatic hypotension, hallucinations, and impulse control disorders (British National Formulary [no date]a; Ahlskog 2014; Bloem et al. 2021). However, dopamine agonists may be used in the early stages of PD where symptoms are not affecting quality of life, or later in the course of PD, where either motor symptom fluctuations can no longer be sufficiently controlled with levodopa alone or dyskinesias occur despite optimisation of the levodopa regimen (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b).

3.1.1.3 Monoamine oxidase-B (MAO-B) inhibitors

As with dopamine agonists, levodopa is generally preferred over MAO-B inhibitors, such as selegiline and rasagiline, due to greater clinical effectiveness (Dezsi and Vecsei 2017; National Institute for Health and Care Excellence 2017b). However, MAO-B inhibitors may be used in the early stages of PD, where symptoms do not affect quality of life, or as an adjunct to levodopa, where this alone is insufficient for managing PD symptoms (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). These medicines inhibit the action of monoamine oxidase enzymes, which are involved in the breakdown of dopamine in the brain, and so improve dopamine availability (Dezsi and Vecsei 2017).

3.1.1.4 Catecholamine-O-methyltransferase (COMT) inhibitors

COMT inhibitors inhibit the action of catechol-O-methyltransferase enzymes that are involved in the peripheral breakdown of levodopa, and therefore increases the amount of levodopa available to cross the blood-brain barrier (Müller 2015). Such agents are administered alongside levodopa to reduce fluctuations in motor symptoms (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b).

3.1.1.5 Advanced PD

In advanced PD, where symptoms remain inadequately controlled, more consistent symptom control may be achieved with continuous administration of dopamine agonists, either subcutaneously (i.e. apomorphine infusion) (Carbone et al. 2019), or intestinally (i.e. using Duodopa®, a form of levodopa administered via a pump as an intestinal gel) (British National Formulary [no date]a; Nyholm 2012). Apomorphine subcutaneous injections may also be used to limit off-periods between levodopa doses (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b; Carbone et al. 2019). Meanwhile, amantadine may be used to reduce the severity of dyskinesias as, alongside its dopamine agonistic activity, it reduces glutamatergic signalling, an increase in which contributes to the greater excitatory signalling in the direct motor pathway of the brain in PD that may result in dyskinesias (Sharma et al. 2018). Finally, if symptoms remain inadequately controlled despite optimal pharmaceutical therapy, surgical management with Deep Brain Stimulation (DBS) may be considered (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b).

3.1.2 Dopaminergic medicine regimens

The types of dopaminergic medicines used by individuals with PD varies. For example, a study examining the medicine regimens of 175 neurology clinic patients who had been taking levodopa for more than four years found 82% used another type of dopaminergic medicine, with 65% prescribed a dopamine agonist, 55% a COMT-inhibitor, 36% an MAO-B inhibitor and 9% using amantadine (Nyholm and Stepien 2014). Conversely, an English study of 91 care home residents and 286 individuals living in the community with PD or

parkinsonism found prevalence rates of 13% and 39% for dopamine agonist use, 2% and 24% for COMT use, 1% and 12% for MAO-B use, and 4% and 7% for amantadine use in care homes and the community, respectively (Hand et al. 2016).

3.1.2.1 Levodopa Equivalent Dose (LED)

Due to the complexity and variance in regimens between individuals with PD and for the same individual over time, the doses of dopaminergic medicines are often converted to a Levodopa Equivalent Dose (LED) to allow for comparison between different regimens (Gerlach et al. 2012). This is completed using conversion factors for dopaminergic medicines to calculate an approximate equivalent dose of immediate-release levodopa (Tomlinson et al. 2010). Previous research examining the daily LED of individuals with PD has found a lower LED in care home residents compared to individuals living in the community, with reported medians of 400mg and 657.5mg, respectively (Hand et al. 2016). However, other studies in the care home setting have reported a higher average LED, with a mean of 526.6mg reported in an English study (Walker et al. 2014), and 673mg in a Dutch study of nursing homes (Weerkamp et al. 2012). It is notable that these report means, as it can be hypothesised that a right skew may explain some of this difference.

Original research on LED estimates have been collated in a previous systematic review by (Tomlinson et al. 2010), with manufacturer reports and clinical trial results used in the absence of other published research, to produce a single table of conversion factors for each dopaminergic medicine. The researchers suggest this is used as a standard approach for producing LEDs to allow better replicability between future studies (Tomlinson et al. 2010).

3.2 AIM

The aim of this chapter is to identify individuals with PD within the core dataset (described in Chapter Two: Core Dataset Creation), using dopaminergic medicines as a proxy, and to:

1. Estimate the prevalence of PD within the core dataset
2. Examine demographic variables of age and sex for individuals prescribed dopaminergic medicines and compare this to the care home population of the core dataset
3. Outline the prevalence of prescribing and use of different types of dopaminergic medicines
4. Evaluate the frequency of administration of dopaminergic medicines
5. Estimate the average prescribed daily LED

3.3 METHODOLOGY

The core dataset produced using the methodology outlined in Chapter Two: 'Core dataset creation' was used as the basis for further analysis presented in this Chapter. Data was extracted from SQL using SSMS v18 (Microsoft 2019) and analysed using Microsoft Excel 365 (Microsoft [no date]) and R v3.6.1 (RStudio 2021; R Core Team 2019).

3.3.1 Dopaminergic medicine identification and classification

The electronic medicines administration record (eMAR) database used reported medicines under their Virtual Medicinal Product (VMP) name, grouped by BNF category. The VMP name is a standardised dm+d name given for a medicine that includes the generic name (i.e. non-brand), the strength, and the form of the medicine (NHS Business Service Authority [no date]). A list of VMP names used under the BNF chapter 'Dopaminergic drugs used in parkinsonism' were extracted from the database. These were mapped to Virtual Therapeutic Moieties (VTM – a name based on the medicines active ingredient) names and grouped into categories of 1) levodopa 2) levodopa + COMT inhibitors 3) COMT inhibitors 4) MAO-B inhibitors and 5) dopamine agonists (see Appendix 5 for further details on categorisation of Dopaminergic medicines). Anticholinergic medicines were not examined in this analysis. The decision to exclude these was due to the use of these also

in the management of other conditions, such as the treatment of extrapyramidal symptoms associated with antipsychotic use, alongside low levels of use in PD due to comparatively poor efficacy. This exclusion has been applied in previous research on PD (Tomlinson et al. 2010; Lertxundi et al. 2017; Skelly et al. 2017).

Medicines were included where they were prescribed for the entire 28-day period studied, except for cabergoline. As this is not recommended for use in PD unless management with levodopa and non-ergot-derived dopamine agonists has failed, and may also be used for hyperprolactinaemic disorders, this was only included where the individual was also prescribed concurrent levodopa (British National Formulary [no date]b; National Institute for Health and Care Excellence 2017b). No individuals prescribed cabergoline met this criterion, therefore a sensitivity analysis was conducted to check for individuals prescribed cabergoline during the study period who had any recorded history of prescribed use of any other dopaminergic medicine. Equally, no individuals were identified.

3.3.2 Demographic analysis

The core dataset (created in Chapter Two) was filtered for dopaminergic medicines. This was used as a proxy to estimate the average age and male to female ratio[6] of individuals with PD within the core dataset; the proportion of care homes providing services to individuals with PD; and the prevalence of PD in this care home population. Differences between the average age and male to female ratio of individuals on dopaminergic medicines compared to the findings for the entire population of the core dataset were assessed for statistical significance with z-test (conducted in Microsoft Excel 365 (Microsoft [no date])) and chi-squared test (conducted in R v3.6.1 (RStudio 2021; R Core Team 2019)), respectively, with a significance level of 0.05 set a priori. Finally, an assessment was made for the number of individuals on dopaminergic medicines under the age of 65 years and over the age of 105 years who were excluded in the creation of the core dataset to help build an understanding of the impact this may have on the results.

[6] Using Title as a proxy. See Chapter Two: 'Core dataset creation' for further details.

3.3.3 Dopaminergic medicines

3.3.3.1 eMAR schedule for administration

Medicines recorded on the eMAR device may be set up to be scheduled for administration based on a fixed schedule (regular medicines), to be administered as needed (as required medicines), or a combination of the two. For regular medicines, the date and time each dose is required is recorded and the care home staff are prompted to administer doses at these times using the eMAR device. The result of the administration attempt for each dose is recorded as either 1) administered 2) not administered (and reason why) or 3) missed (no attempt made).

3.3.3.2 Dopaminergic medicines use

The number of active dopaminergic medicines and individuals prescribed these was extracted from the core dataset. The proportion of dopaminergic medicines recorded as regular medicines, and the number of individuals prescribed levodopa only; other dopaminergic medicines only; or a combination of levodopa and other dopaminergic medicines was examined.

Furthermore, an assessment was made for evidence of administration activity for these medicines, by joining the core dataset to the administration table on the resident – medicine unique ID, and filtering on a date of administration between the 19/06/2020 and the 16/07/2020, inclusive, to obtain the number of medicines and individuals for which an administration attempt had been made (whether or not successful).

3.3.3.3 Estimation of required frequency of administration

The mean numbers of time an administration was required each day for regular dopaminergic medicines was calculated at individual level using SQL code. This was completed using common table expressions (allowing temporary tables to be created on which further analysis can be completed (Microsoft 2017d)), by performing a distinct count of the times required grouped by the date required and resident ID. An average of this count was then taken, grouped only by the resident ID, rounded to the nearest whole number. The resulting averages were exported to Microsoft Excel 365 (Microsoft [no date]). Two further extractions for frequency of scheduled administration were performed using the same SQL code, filtered for

levodopa medicines including Stalevo®[7] and other dopaminergic medicines, respectively. As this represents discrete data with a right skew, test for statistical significance in the difference in distribution is reported using Wilcoxon Sum Rank test (conducted using R v3.6.1 (RStudio 2021; R Core Team 2019)).

3.3.3.4 Estimation of required daily LED

As the quantity required was not provided within the database, this was estimated as the mode for each resident – medicine – time required combination using the stock level. This was completed by subtracting the current stock level from the stock level recorded for the previous administration where a dose of a regular medicine was administered to return the quantity administered. To facilitate this analysis, a new table containing administration records for regular dopaminergic medicines required or attempted during the study period was created (PD table), with added calculated columns for stock level at the previous administration and the LED for the medicine, based on the medicines strength, for 1) levodopa and 2) other dopaminergic medicines.

The total administrations for each resident – medicine – time required – quantity administered combination was then calculated, and the most common quantity administered for each resident – medicine – time required combination was selected. Administrations where the stock level was higher than the stock level recorded at the previous dose were excluded. This may occur because of either receipt of medicine supply from the dispensing pharmacy or manual update of the record at the care home following a stock take.

Conversion factors as reported in a systematic review by Tomlinson et al (Tomlinson et al. 2010) were used to produce LED values based on the strength of medicines (except for COMT inhibitors), which were mapped to the relevant VMP names in SQL. These were multiplied by the estimated

[7] Stalevo® is a combination medicine containing levodopa, carbidopa and entacapone British National Formulary. [no date]d. *Levodopa with Carbidopa and Entacapone*. National Institute for Health and Care Excellence. Available at: https://bnf.nice.org.uk/drug/levodopa-with-carbidopa-and-entacapone.html [Accessed: 25/09/2021].

quantity required for each resident – medicine – time required combination to produce a total daily LED for 1) levodopa and 2) other dopaminergic medicines (excluding COMT inhibitors). Where liquids were administered, the estimated quantity required was adjusted to account for the volume at which the strength was recorded in the VMP name. For example, for 'Amantadine 50mg/5ml oral solution sugar free', the estimated quantity required was divided by 5, such that where 20ml were administered, this equates to a dose of 200mg.

As COMT inhibitors work by reducing the peripheral breakdown of levodopa, and hence augmenting its central availability, the conversion factor used for these medicines was based upon the daily levodopa LED. Therefore, for individuals using COMT inhibitors, the additional daily LED provided by COMT inhibitors was estimated by multiplying the total levodopa LED by 0.33 (Tomlinson et al. 2010). Finally, the total LED was calculated as the sum of these for 1) levodopa 2) other dopaminergic medicines (excluding COMT inhibitors) and 3) COMT inhibitors.

The average estimated required daily LED was calculated for 1) all individuals using dopaminergic medicines 2) individuals using levodopa and 3) individuals not using levodopa. As a right skew was seen, test for statistical significance in the difference in distribution between the latter two groups using Wilcoxon Sum Rank test (conducted using R v3.6.1 (RStudio 2021; R Core Team 2019)) is reported.

3.4 RESULTS

3.4.1 Demographic analysis

375 of the 9,082 individuals within the core dataset had one or more dopaminergic medicine identified as active throughout the study period, equating to a prevalence rate of 4.13%. Over a half of care homes provided services to one or more of these individuals (186 of 310, 60%). A comparison of the mean age and male to female ratio of individuals on dopaminergic medicines compared to the full population of the core dataset is presented in Table 3.1.

Table 3.1: Comparison of the mean age and male to female ratio of individuals using dopaminergic medicines (PD subset) compared to the full care home population of the core dataset

	PD Subset	Core Dataset	P-Value
Mean age (95% confidence interval)	83.31 (82.60 – 84.01)	85.82 (85.76 - 85.88)	<0.001
% Male	45%	29%	<0.001

6 individuals under the age of 65 years and 5 individuals over the age of 105 years using dopaminergic medicines during the study period were excluded from the core dataset. This includes individuals with a Year of Birth of 1900, which is suggestive that the Date of Birth had not been recorded on the eMAR system[8].

[8] SQL uses a default value of 01/01/1900 for date fields Microsoft. 2017a. *date (Transact-SQL)*. Available at: https://docs.microsoft.com/en-us/sql/t-sql/data-types/date-transact-sql?view=sql-server-2016 [Accessed: 25/09/2021]. .

3.4.2 Dopaminergic medicines use

A total of 592 active (prescribed) dopaminergic medicines across 375 individuals were identified within the core dataset, the majority of which were recorded as regular medicines (571 of 592, 96.45%). Less than 2% of individuals had no regular dopaminergic medicine recorded. Only 6 of the 21 dopaminergic medicines that were not recorded as regular medicines were administered during the study period, with an average of 61.5 administrations across 24 days recorded for these medicines.

90% of individuals were prescribed levodopa, and around three-quarters of individuals were not prescribed any other dopaminergic medicines (Figure 3.2). The most commonly prescribed type of dopaminergic medicine after levodopa was dopamine agonists, followed by COMT inhibitors, and MAO-B inhibitors, with 71 (18.93%), 21 (5.60%) and 16 (4.27%) individuals prescribed these, respectively (Table 3.2). 9 individuals (2.40%) were prescribed amantadine.

547 of the 592 (92.40%) active dopaminergic medicines, and 541 of the 571 regular medicines had at least one scheduled administration recorded during the study period (94.75%), with the majority required every day throughout the study period (517 out of 571, 90.54%). However, 13 individuals had some days for which no there was no administration record present. This affected one day for 6 of these individuals and more than one day for the other 7 individuals (overall mean of 5.14, median of 3). Furthermore, 20 of the 375 individuals had either no required administrations or administration attempts recorded throughout the entire study period, or no regular medicines recorded, leaving 355 individuals for subsequent analyses examining Levodopa Equivalent Doses (LEDs) and dose omissions.

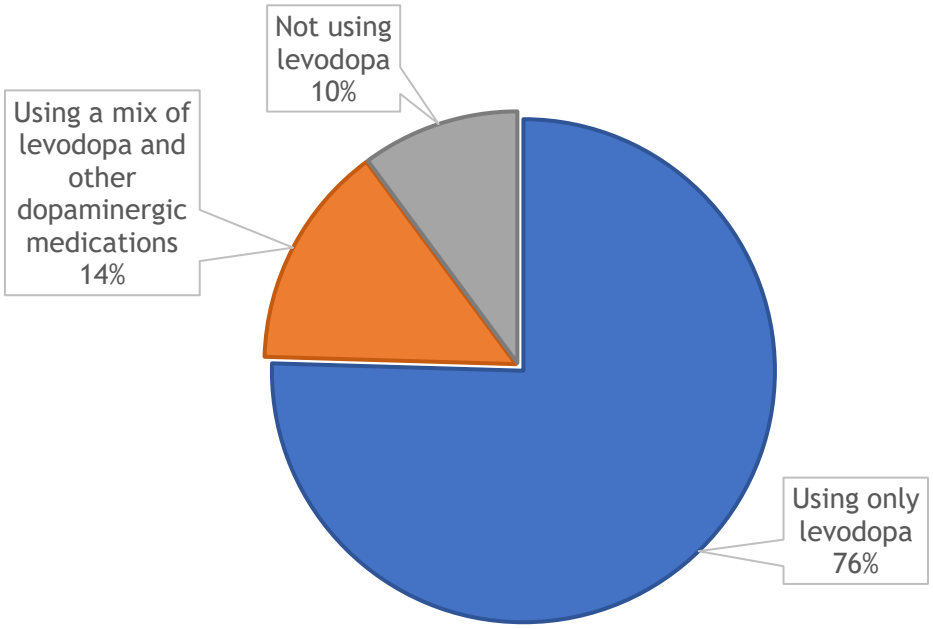

Figure 3.2: Levodopa use

Table 3.2: Number and percentage of dopaminergic medicines and individuals by medicine type

Medicine type	Medicines (%)	Individuals (%)
Levodopa	487 (82.26)	337 (89.87)
Dopamine agonist	82 (13.85)	71 (18.93)
MAO-B	16 (2.70)	16 (4.27)
COMT	22 (3.72)	21 (5.60)
Total	**592**	**375**

3.4.2.1 Estimation of required frequency of administration

The mean number of administrations scheduled per day per individual for regular dopaminergic medicines was 3.55 (95% CI 3.40 – 3.70). The majority of individuals had between 3 and 4 administrations scheduled per day, with a median of 3 (interquartile range 3 – 4), and a right skew of outliers (Figure 3.3). A statistically significant difference in distribution was seen for levodopa compared to other dopaminergic medicines (P<0.001), with medians of 4 (interquartile range 3-4) and 1 (interquartile range 1-2), respectively.

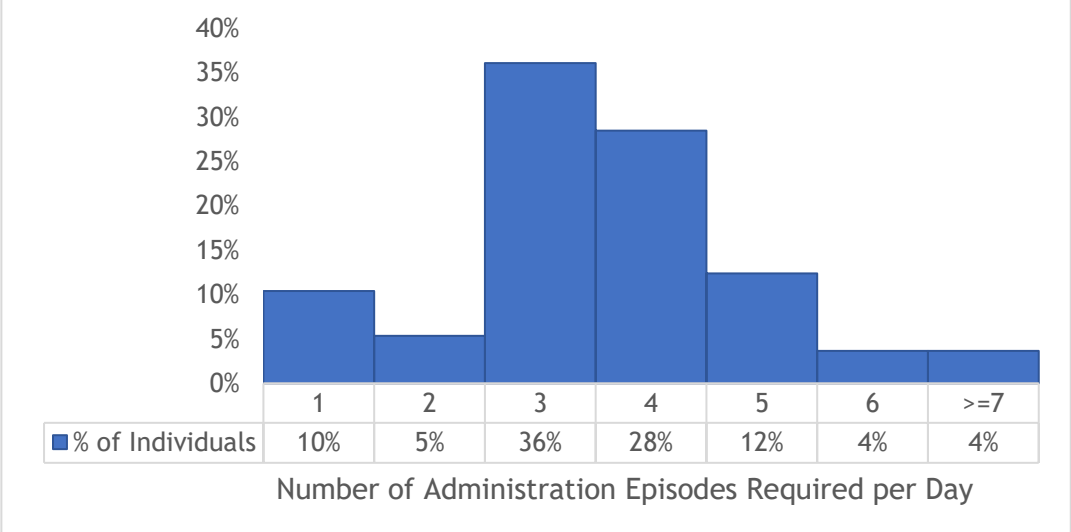

Figure 3.3: Estimation of the frequency of administration for regular dopaminergic medicines

3.4.2.2 Estimation of required daily LED

Across the 355 individuals with regular dopaminergic medicines scheduled for administration during the 28-day period examined, the mean estimated daily LED required for regular dopaminergic medicines was 403.36mg (95% confidence interval 373.49mg – 433.23mg). This showed a right skew (Figure 3.4), with a median of 340mg (interquartile range 200mg – 500mg). A statistically significant difference in distribution was seen for daily LED for individuals using levodopa compared to those who were not (P<0.001), with medians of 375 (interquartile range 250mg – 550mg) and 88mg (interquartile range 22.5mg – 180mg), respectively.

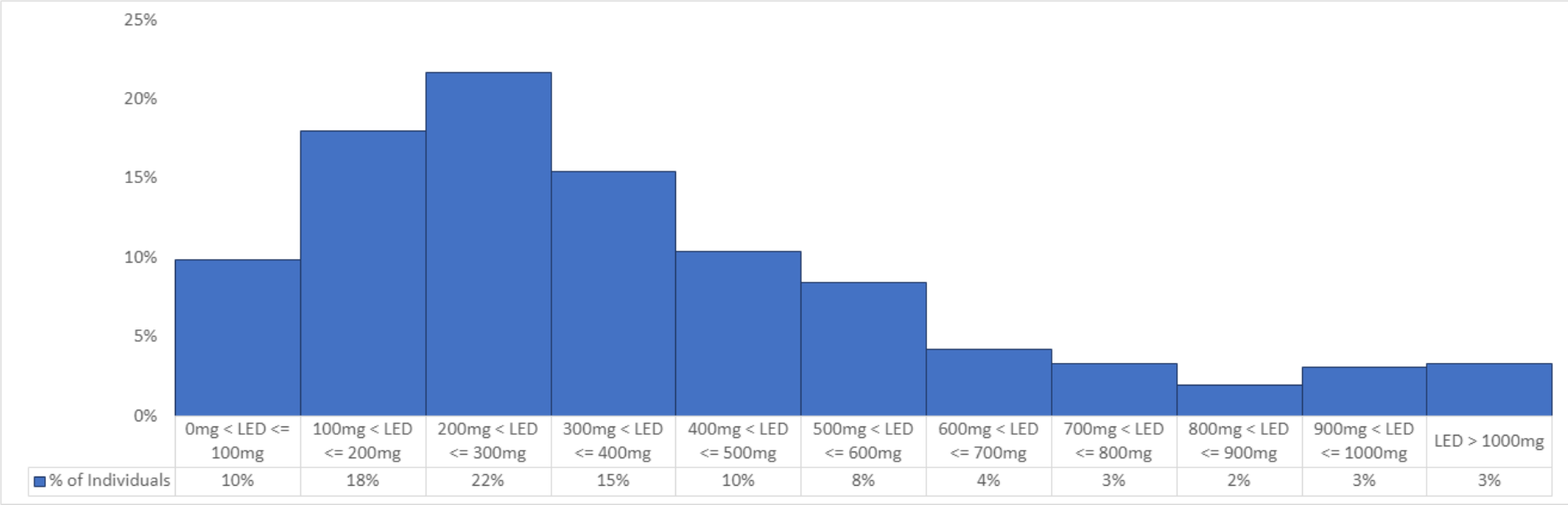

Figure 3.4: Estimation of the required daily Levodopa Equivalent Dose (LED, mg). Dopaminergic medicines scheduled for regular administration were converted to an approximate LED, the equivalent dose of immediate-release levodopa in milligrams (Tomlinson et al. 2010). These were used to estimate the total daily LED required for each of the 355 individuals with regular dopaminergic medicines scheduled for administration during the 28-day period examined.

3.5 DISCUSSION

3.5.1 Parkinson's disease

3.5.1.1 Estimated prevalence of PD

The estimated prevalence rate of PD in the core dataset in this study was around 4%. This is greater than the estimated prevalence of up to around 2% within the general population, dependent on age and sex (Wickremaratchi et al. 2009; Parkinson's UK 2017; Doyle 2018). As PD has been found to be associated with a greater likelihood of requiring care home services (Nihtilä et al. 2008), this may explain a higher prevalence rate of PD within the care home setting. Where the prevalence of PD has been examined in the care home setting in previous research, variable results have been found, with estimates ranging from 1.6% to 6.8% identified (Larsen 1991; Mitchell et al. 1996a; Lapane et al. 1999; Porter et al. 2010). Possible reasons for this may include international differences, for example in healthcare systems, or changes over time.

Around 60% of care homes within the core dataset had at least one resident prescribed a dopaminergic medicine during the study period. This demonstrates that PD is a condition commonly encountered by a large proportion of care homes, rather than being confined to specialist homes. Coupled with a high turnover rate seen within care homes (Costello et al. 2020), this may make specialist training of staff caring for individuals with PD difficult to maintain in this setting.

One potential approach for overcoming this challenge could be the introduction of PD specialist care homes. Where studied in the acute setting, such clustering of PD cases has been found to be statistically significantly associated with fewer medicine administration and prescribing errors, better patient experience, and a shorter length of stay (Skelly et al. 2014). However, it should be noted that this was a small pilot study with fewer than 30 cases (Skelly et al. 2014). Furthermore, qualitative research has uncovered perceived drawbacks of the introduction of PD specialist care homes, including resident fears of confrontation with the future of their PD condition; increased travel for visitors and caregivers; and increase in the

physical and mental demand of work for staff (van Rumund et al. 2014). Only one PD specialist unit in Europe could be identified for the care home setting, and only a descriptive study for this could be found, with no statistical assessment of the impact of the introduction of this (Lökk 2011).

Another approach to improving PD specialist knowledge within the care home setting could be improved access to PD specialist clinicians, including PD nurses. Such healthcare professionals have been found to be a resource valued by both care home residents and staff, with access to PD specialists associated with improved quality of life of individuals with PD living in care homes (Jarman et al. 2002; Trend et al. 2002; Stocchi and Bloem 2013; van Rumund et al. 2014; Bloem and Stocchi 2015; Hellqvist and Berterö 2015). Further research is needed to explore the feasibility and potential benefits of such approaches within English care homes.

3.5.1.2 Demographics

3.5.1.2.1 Age

The average age of individuals in the PD subset was 83. This was found to be statistically significantly lower than average age across the full care home population of the core dataset presented in Chapter Two (83 vs 86 years, $P<0.001$), suggesting individuals may enter care homes at a younger age than older adults requiring care for other reasons. In addition, the average age in the PD subset of this analysis was higher than estimates for this across all individuals with PD (McLean et al. 2017; Weir et al. 2018). A similar disparity is seen in previous research examining PD medicine use in both the care home and community setting (mean ages of 82.4 and 75.9, respectively) (Hand et al. 2016). This supports the findings of previous research, in which age was found to be a statistically significant predictor of nursing home placement in individuals with PD (Aarsland et al. 2000). This may be due to an increased severity in symptoms and greater impairments in motor function as the condition progresses.

Despite this, the average age found in this analysis is towards the upper end of previous estimates for individuals with PD living in care homes (Mitchell et al. 1996b; Lapane et al. 1999; Aarsland et al. 2000; Buchanan et al. 2002;

Weerkamp et al. 2012; Walker et al. 2014). This may be a result of differing inclusion criteria. For example, individuals under the age of 65 years excluded in the analysis in this chapter. However, as only 6 individuals were excluded for this reason, it is unlikely this had a large impact. Another explanation may be that the age of PD residents is increasing over time, as seen for the wider older adult care home population (Office for National Statistics 2003,2013; Smith 2014). Further research is needed to explore this.

3.5.1.2.2 Sex

As expected, a significantly greater proportion of individuals using dopaminergic medicines were male compared the full care home population of the core dataset (45% vs 29%, P<0.001). However, despite PD being more common in men (McLean et al. 2017; Weir et al. 2018), a slightly higher proportion of females was found in this analysis. Similar findings have been reported in previous research (Lapane et al. 1999; Buchanan et al. 2002; Weerkamp et al. 2012; Walker et al. 2014). This suggests that women with PD may be more likely to require care home services than men. The reason for this should be explored. Possible explanations may include the higher life expectancy seen in women (Coombs et al. 2019), alongside an association between older age and care home residency in individuals with PD (Aarsland et al. 2000; Ishihara et al. 2007).

3.5.2 Dopaminergic medicines

By far the most commonly used type of dopaminergic medicine in this analysis was levodopa, with around 90% of individuals prescribed this. Similar results have been reported for individuals with PD in Dutch nursing homes (92%) (Weerkamp et al. 2012). The use of other dopaminergic medicines in this analysis was higher than previous findings in English care homes (Hand et al. 2016), with the exception of amantadine, but lower than seen in the community setting (Nyholm and Stepien 2014) (Hand et al. 2016). Similarly, a lower use of other dopaminergic medicines in the care home setting has been reported in previous research (Hand et al. 2016). An examination of the reason for this is needed. Possible explanations may include the discontinuation of other dopaminergic medications due to adverse effects (Ahlskog 2014; Abbasi et al. 2020) (British National Formulary [no date]a;

Bloem et al. 2021). However, another explanation could be a lower frequency of review of dopaminergic medicines in the care home setting, for example due to difficulties in attending outpatient appointments. This is supported by previous research, which has found evidence of possible undertreatment. In this study, 44% of individuals in the nursing homes examined experienced significant 'off-period' of uncontrolled PD symptoms (Weerkamp et al. 2012). The majority of these had not had their PD medicines amended since admission (Weerkamp et al. 2012).

3.5.3 Frequency of administration and daily LED

Analysis of the frequency of administration in this chapter found a lower average number of doses administered per day compared to previous research in the community setting (3.76 compared to around 4-8, respectively) (Hutton et al. 1988; Sivertsen et al. 1989; Hutton and Morris 1991; Damier et al. 2008; Grosset et al. 2009; Nyholm and Stepien 2014). Similarly, estimates for the average daily LED found in this analysis were lower than those reported in both the care home and community setting (Weerkamp et al. 2012; Walker et al. 2014; Hand et al. 2016). A lower daily LED has been previously reported for the care home population compared to individuals living in the community (Hand et al. 2016). This may be a result of attempts to manage adverse effects of medications by reducing the total levodopa dose administered (Kadastik-Eerme et al. 2017). Furthermore, as a negative association between age and dose fractionation has been reported (Nyholm and Stepien 2014), a possible explanation for the lower levels of dose fractionation seen in this analysis may be the older age represented (see 3.5.1.2.1: Age). Further work is needed to examine this.

3.5.4 Limitations

3.5.4.1 Information not available through the data source used

The main limitation of this analysis is the absence of clinical notes. As a result, assessment for confirmation of idiopathic PD as opposed to other causes for parkinsonism, and evaluation of PD severity was not possible. In addition, the use of dopaminergic medications as a proxy for PD may fail to identify some individuals who are no longer using medicines due to poor efficacy or intolerable adverse effects. This accounted for around 5% of

individuals with parkinsonism in a previous study of English care homes (Walker et al. 2014).

Meanwhile, although the medicines included in this analysis are commonly used in PD, some may also be used for other indications. For example, ropinirole, pramipexole and rotigotine may be used in the management of restless leg syndrome (Harding and Cox 2015), and amantadine may be used for managing fatigue in multiple sclerosis or prophylaxis in influenza (British National Formulary [no date]c). This can be considered fairly likely for 9 individuals taking pramipexole, and 5 individuals taking ropinirole only in the evening or at night, exclusion of which would decrease the proportion of individuals not using levodopa from 10% to 6.5%. Therefore, in light of these limitations, replication of this study with verification of clinical diagnosis and indication for dopaminergic medicine use should be undertaken to validate the findings outlined in this chapter.

Another limitation of this analysis is the absence of data on the quantity of each medicine to be administered for each required dose in the study database. To enable calculation of the average daily LED required to be undertaken, changes in stock level were used to estimate the quantity administered in this analysis. To reduce the impact of changes to stock levels between the administration of doses due to either stock takes or receipt of new supply, the most common stock change for each resident – medicine – time required combination was used in place of the mean for calculation of the required daily LED. However, research verification of the accuracy of estimates of quantity administered produced in this way, for example through comparison with records held by the care homes, is outside the scope of this thesis. Furthermore, such methodology will be insensitive to detecting possible changes in the required dose during the study period, for example following clinician review.

3.5.4.2 Data challenges requiring further examination

3.5.4.2.1 Individuals with no administrations recorded

Although most individuals had records of administration for dopaminergic medicines recorded daily throughout the study period, a minority of

individuals had no record of administration for dopaminergic medicines on all (18 individuals) or some (13 individuals) days during the study period. As almost all dopaminergic medicines were required to be administered regularly (96.5%), this is unexpected. As the date and time at which regular medicines are required is scheduled on the eMAR device and recorded in the administration table whether or not an administration attempt takes place, the absence of any record of attempt for these implies that such medicines were not required on these days.

No administration was recorded as either scheduled or administered on one or more days during the study period for almost 10% of dopaminergic medicines (54 out of 571) in this analysis, including 30 medicines with no administration record throughout the entire 28-day period. Future research should be undertaken to explore the reason for this. Possible reasons may include temporary deactivation of prompting for scheduled doses, for example following admission to a hospital. Another possible explanation may be data quality issues, for example failure of archiving individuals no longer resident at the care home. Identification of the exact reason for this was outside of the scope of this thesis but should be explored in future work. This may require the use of care planning notes or liaison with the care home to uncover the reason for these findings. Furthermore, it should be noted that if these cases represent individuals who are no longer residing at the care home, the inclusion of these may have impacted on demographic and prevalence estimates. However, as this affected a minority of individuals, the effect of exclusion of these would be expected to be small.

3.5.4.2.2 Identifying scheduled doses where medicines may also be used ‘as required’

As noted previously, most dopaminergic medicines were recorded as ‘regular’ (96.5%). Medicines not recorded as regular on the eMAR device represent those that are either 1) used ‘as required’ (not scheduled) or 2) used as a combination of scheduled dosing with additional administrations ‘as required’. Although a minority (<2%) of individuals had no regular dopaminergic medicines recorded, not all of these fell within the latter category. Only a small proportion of medicines not recorded as ‘regular’

were administered during the study period (6 out of 21), and all of these were recorded as being used as a combination of scheduled dosing within additional administrations 'as required'. These were administered on an average of 24 of the 28 days during the study period. No medicines recorded for use on a purely 'as required' basis were administered during the study period. However, exploration of whether this was appropriate (i.e. the individual had good symptom control without the use of these) was outside the scope of this analysis.

As the date and time an administration attempt is made is recorded in the date required field when medicines are used 'as required', it is difficult to separate scheduled doses from 'as required' doses where a medicine may be administered in either way. The addition of a flag in eMAR data where doses are scheduled should be considered for medicines that may be used both with scheduled dosing and 'as required'. If this is not possible, recording of seconds in the time field (e.g. time 09:37.33) should be considered as a proxy for truly 'as required' doses, as it is unlikely doses would be scheduled to this level of precision.

3.6 CONCLUSION

The results of this chapter suggest that PD is a condition commonly encountered by staff working within care homes in England. Individuals with PD living in care homes appear to show distinct demographic characteristics both compared to the general older adult care home population, and individuals with PD living in the community. Furthermore, as in previous research, differing patterns of medicine use were seen in this analysis of care home residents compared those described for community populations with PD. Therefore, this supports the analysis of these settings as distinct groups. As individuals with PD are dispersed across many care homes, the use of remotely accessible data, such as that provided by eMAR systems, may help facilitate research and clinical monitoring of this group. However, the limitations outlined should be considered and addressed where needed to improve the scope and quality of analyses that is possible.

4 DOSE OMISSIONS OF DOPAMINERGIC MEDICINES

4.1 INTRODUCTION

As outlined in Chapter One, dose omissions are a type of medicine administration error (MAE) where a dose of a prescribed medicine is not administered (Keers et al. 2013). As PD is currently an incurable condition, for which the motor symptoms are managed using dopaminergic medicines, omission of these medicines can result in worsening of symptoms (Magdalinou et al. 2007). No studies examining dose omissions of PD medicines in the care home setting were identified.

4.1.1 Dose omissions of PD medicines in the acute setting

4.1.1.1 Prevalence of dose omissions

Although no studies exploring the prevalence of dose omissions for PD medicines in the care home setting were identified, these have been reported in the acute setting (Derry et al. 2010; Hou et al. 2012; Nageshwaran et al. 2013; Skelly et al. 2014; Martinez-Ramirez et al. 2015; Lertxundi et al. 2017; Hunt et al. 2018). These have found varying results, with prevalence rates for dose omissions of PD medicines ranging from around 3% (Lertxundi et al. 2017) to 20% (Skelly et al. 2014). In addition, dose omissions have been found to be more common nearer the time of admission to hospital (Hou et al. 2012), with delays of up to 72 hours in administering the first dose of a PD medicine reported (Nageshwaran et al. 2013). However, it is worth noting that some of these studied relatively small samples sizes, with fewer than 60 cases examined (Derry et al. 2010) (Skelly et al. 2014).

Monitoring of the prevalence of dose omissions of PD medicines in the UK is currently challenging because information on the occurrence of these is not routinely collected. This is noted by Parkinson's UK in their 'Get it On Time' report (Parkinson's UK 2019), in which they found that information on patient safety incidents in relation to dose omissions or delay in administration of PD medicines was frequently not recorded in the incident reporting systems of hospital trusts. Over half of the 112 respondents of a Freedom of Information (FOI) request stated that such information was not available, either because these safety incidents were not recorded (17%) or were not recorded by clinical condition (41%). Of the 47 respondents that were able to provide

information, 657 patient safety incidents were reported for the financial year 2018/19. As a result of these findings, Parkinson's UK have called on the Care Quality Commission (CQC) to make dose omissions for PD medicines a 'never event' [9] to promote a reduction in occurrence and better reporting (Parkinson's UK 2019).

4.1.1.2 Consequences of dose omissions

Omission of PD medicines may increase the occurrence of off-periods, where PD symptoms worsen as a result of reductions in the plasma concentrations of levodopa (Ahlskog 2014). These become more likely over the course of PD, as a pattern of shorter duration of therapeutic response to levodopa develops, and the response therefore more closely matches the administration schedule (Ahlskog 2014). Where doses of PD medicines are omitted, these may affect the individuals functioning and symptoms, with worsening of off-periods (42%), anxiety (29%), immobility (26%), pain (16%) and dysphagia (10%) reported by respondents of a patient survey questionnaire in the UK (Skelly et al. 2014). Furthermore, omissions of PD medicines may result in serious harm, including akinetic crisis and neuroleptic malignant syndrome (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). These are life-threatening conditions causing fever, muscle rigidity and neurological dysfunction (Berman 2011; Kaasinen et al. 2014; Whitman et al. 2016). Other sequelae of PD medicine dose omissions reported include patient transfers to intensive care, hip fractures, severe rigidity, dehydration and constipation and the cancellation of physiotherapy and rehabilitation appointments (Magdalinou et al. 2007).

Omission of PD medicines has also been found to be associated with increase length of hospital stay (Martinez-Ramirez et al. 2015; Lertxundi et al. 2017) and mortality (Lertxundi et al. 2017). For example, in the Basque country,

[9] The NHS defined 'never events' as "serious incidents that are entirely preventable because guidance or safety recommendations providing strong systemic protective barriers are available at a national level, and should have been implemented by all healthcare providers." NHS England. 2018. *Revised Never Events policy and framework*. NHS England. Available at: https://www.england.nhs.uk/patient-safety/revised-never-events-policy-and-framework/ [Accessed: 18/09/2021].

inappropriate omission of dopaminergic medicines was found to be associated with a four day increase in the median length of stay and a greater odds of mortality (adjusted odds ratio 1.92) (Lertxundi et al. 2017). Furthermore, a very high, statistically significant odds ratio was found for mortality where levodopa was completely omitted (5.49), however this was no longer statistically significant when individuals dying within 72 hours of admission were excluded (Lertxundi et al. 2017). Similarly, a US study reported a statistically significant increase in length of stay where an individual experienced an omission or delay in the administration of dopaminergic medicines (mean 8.2 days vs 3.6 days) (Martinez-Ramirez et al. 2015). However, no statistically significant association with length of stay was found when this was examined in an English hospital (Skelly et al. 2017).

4.1.1.3 Reasons for dose omissions

Many reasons for dose omissions of PD medicines in the acute setting have been reported. These include the medicine not being available (Derry et al. 2010; Martinez-Ramirez et al. 2015; Lertxundi et al. 2017; Skelly et al. 2017; Hunt et al. 2018) or not prescribed (Skelly et al. 2014); the patient being nil-by-mouth (NBM) (Derry et al. 2010; Skelly et al. 2014; Martinez-Ramirez et al. 2015; Lertxundi et al. 2017; Skelly et al. 2017), absent (Derry et al. 2010; Lertxundi et al. 2017) or declining the dose (Derry et al. 2010; Skelly et al. 2017); or a result of a nursing decision (Skelly et al. 2014). In some cases, no reason for omission was recorded. For example, a reason was recorded in only around a third of dose omissions and late administrations of PD medicines in a sample of Scottish surgical admissions (Derry et al. 2010), and just 7.2% of dose omissions for levodopa or dopamine agonists in a retrospective study conducted in the US (Martinez-Ramirez et al. 2015).

4.2 AIM

As stated in the introduction, no studies examining dose omissions of PD medicines in the care home setting were identified. Therefore, the aim of this chapter is to explore the prevalence of, and reasons for, dose omissions of dopaminergic medicines, by examining:

- The proportion of doses successfully given, as a proportion of the total doses scheduled for administration
- Differences between omission rates for levodopa compared to other dopaminergic medicines
- Reasons recorded for omissions of dopaminergic PD medicines

It can be hypothesised that lower levels of dose omissions may be seen in the care home setting, as acute changes in health and other disruptions to the usual medicine regime, for example being nil-by-mouth, would be less common than in the hospital setting. However, both PD and care home residency have been found to be associated with an increased risk of polypharmacy (Shah et al. 2012; Gordon et al. 2014; McLean et al. 2017), which is, in turn, associated with greater odds of dose omissions (Rostami et al. 2019). Furthermore, PD dementia and psychosis, which are more commonly seen in the care home population, may reduce adherence to treatment regimens (Aarsland et al. 2000; Hand et al. 2016).

4.3 METHODOLOGY

For the purposes of the analysis presented in this chapter, regular dopaminergic medicines recorded in the core dataset that were scheduled for administration during the study period were examined using the PD table. For more details on the creation of the core dataset see Chapter Two, for details on the identification of dopaminergic medicines, see Chapter Three, and for details on the PD table see Chapter 3.3.3.4 Estimation of required daily LED. Data was extracted using SQL Server Management Studio (SSMS) v18 (Microsoft 2019).

4.3.1 Prevalence of dose omissions

The prevalence of dose omissions of dopaminergic medicines was calculated as the total number of required doses that were not administered as a percentage of the total opportunities for error (the total number of administrations required during the study period), using counts of distinct Administration IDs. This is in line with the methodology suggested in the National Institute for Health and Care Excellence (NICE) PD Quality Statement 4: "Levodopa in hospital or a care home" (National Institute for Health and Care Excellence 2018). The proportion of individuals encountering one or more dose omission during the study period was calculated in a similar way, using a count of distinct Resident IDs in place of Administration IDs. Finally, the prevalence of dose omissions was calculated for each resident and visualised in Microsoft Excel 365 (Microsoft [no date]) to examine for variation.

All analyses were conducted for all dopaminergic medicines, as well as separate analyses for 1) levodopa medicines including Stalevo® [10] and 2) other dopaminergic medicines. Chi-squared was used to test for a statistically significant difference in overall prevalence rates, and, as data was not normally distributed, Wilcox Sum Rank test used to assess for a statistically significant difference in distribution in the prevalence rates seen at resident level, using R v3.6.1 (RStudio 2021; R Core Team 2019). A significance level of 0.05 was set a priori.

4.3.2 Reasons for dose omissions

An analysis of the reasons recorded for dose omissions of dopaminergic medicines was also undertaken. When a dose is attempted but not administered, care home staff are prompted by the eMAR device to select the reason for this from a pre-specified list. The reasons recorded for omissions of dopaminergic medicines during the study period are recorded in Table 4.1. This includes 'Missing Unknown'. These are the equivalent of

[10] Stalevo® is a combination medicine containing levodopa, carbidopa and entacapone British National Formulary. [no date]d. *Levodopa with Carbidopa and Entacapone*. National Institute for Health and Care Excellence. Available at: https://bnf.nice.org.uk/drug/levodopa-with-carbidopa-and-entacapone.html [Accessed: 25/09/2021].

missing entries (absence of signature) on a paper MAR chart and are recorded when no attempt was made for a required dose, either due to failure to administer the dose, or failure to record this on the eMAR device.

Table 4.1: Categorisation of reasons recorded for dose omissions

Category	Reason
Asleep	Resident Asleep
Declined	Resident Refused
Other	Missing Unknown
	Resident Absent
Stock	Awaiting Stock
	Destroyed/ Damaged
	Stock Unavailable
Withheld	Nausea Vomiting
	Too soon
	Not Required
	Resident too Ill

The number of administrations for each recorded reason was extracted for dose omissions of required regular dopaminergic medicines. These were exported to Microsoft Excel 365 (Microsoft [no date]) for further analysis. Due to low numbers, and to facilitate comparisons with previous research on dose omissions, the reasons for omission recorded in the dataset were categorised into five groups (Asleep, Declined, Withheld, Stock and Other) for visualisation (Table 4.1).

4.4 Results

4.4.1 Prevalence of dose omissions

Within the core dataset, a total of 40,187 required administrations for dopaminergic medicines were recorded during the study period, the majority of which were for levodopa (91.08%). Only one administration record was present for each resident – medicine – date required – time required combination. 2.15% of all doses were omitted, with a slightly higher prevalence for levodopa medicines (Table 4.2). However, this difference was not statistically significant (P=0.079).

Table 4.2: Prevalence of dose omissions

	Administered (%)	Not Administered (%)	Total
Levodopa	35,801 (97.81)	802 (2.19)	36,603
Other	3,522 (98.27)	62 (1.73)	3,584
Total	39,323 (98.85)	864 (2.15)	40,187

On the whole, individuals had the majority of the required doses for regular dopaminergic medicines administered, with 61.13% of individuals experiencing no dose omissions and 90% of individuals having at least 95% of doses administered (Figure 4.1). A median of 100.00% of doses were administered (interquartile range 98.8% - 100.00%). However, a significant minority had a large proportion of doses omitted, with 3.01% of individuals having over 20% of doses omitted.

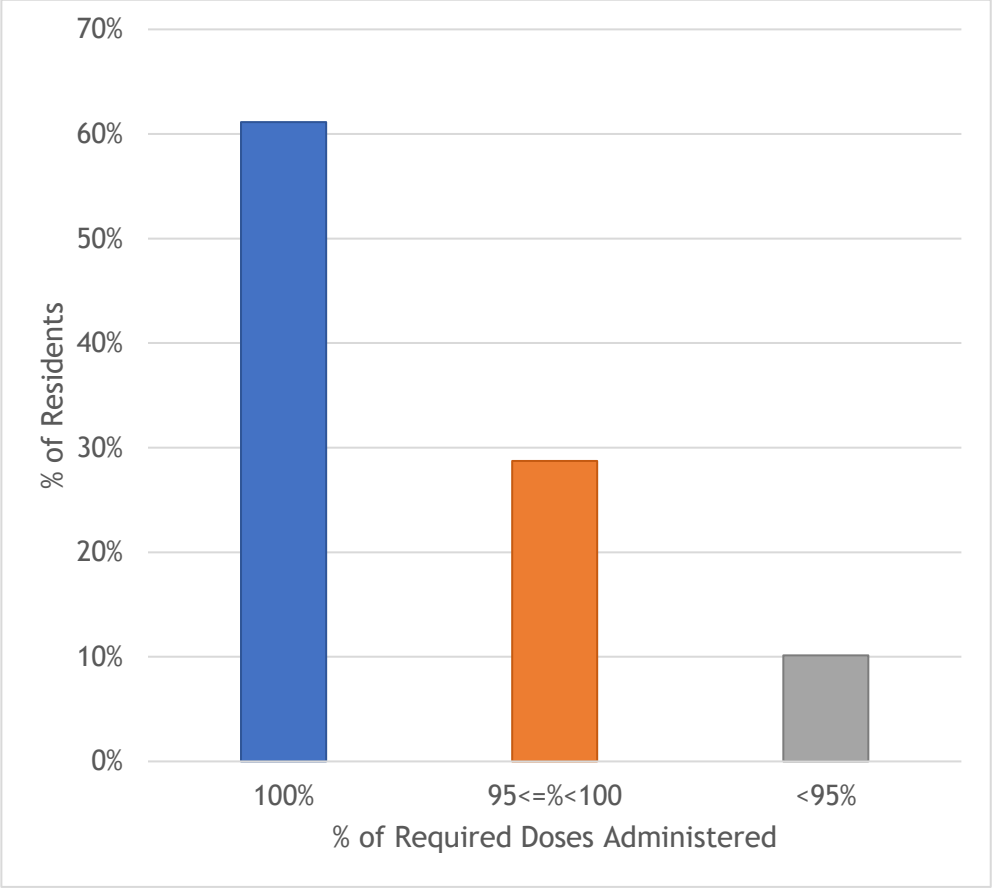

Figure 4.1: Percentage of required doses for regular dopaminergic medicines administered per resident

Individuals were statistically significantly more likely to experience at least one omission of levodopa compared to other dopaminergic medicines (P=0.001, Table 4.3). Furthermore, a statistically significant difference in the distribution of the percentage of doses administered per resident was seen for levodopa compared to other dopaminergic medicines (median 100.00%, interquartile range 98.6% - 100.00% vs median 100.00%, interquartile range 100.00% - 100.00%, respectively; P=0.006). This demonstrates a higher proportion of cases experiencing dose omissions for levodopa medicines.

Table 4.3: Proportion of individuals experiencing one or more dose omission during the study period for levodopa medicines and other dopaminergic medicines

	No omissions (%)	Omissions (%)	Total
Levodopa	190 (59.56)	129 (40.44)	319
Other	63 (79.75)	16 (20.25)	79
Total	253 (63.57)	145 (36.43)	398[11]

4.4.2 Reasons for dose omissions

Figure 4.2 shows the reasons recorded for dose omissions, as a percentage of the total omissions. The most common reason for omission was the resident declining the dose (43.98%), followed by the resident being asleep (22.80%), stock issues (13.31%), other reasons including missing entries and resident absence (10.07% total, 8.68% and 1.39% respectively) and being withheld (9.84%). The most common reason recorded for withholding a dose was 'not required', followed by 'too soon' and resident illness or nausea and vomiting (4.86%, 2.78% and 2.2% of total omissions, respectively).

[11] Total is greater than the total number of residents (355) due to some individuals using both levodopa and other dopaminergic medicines

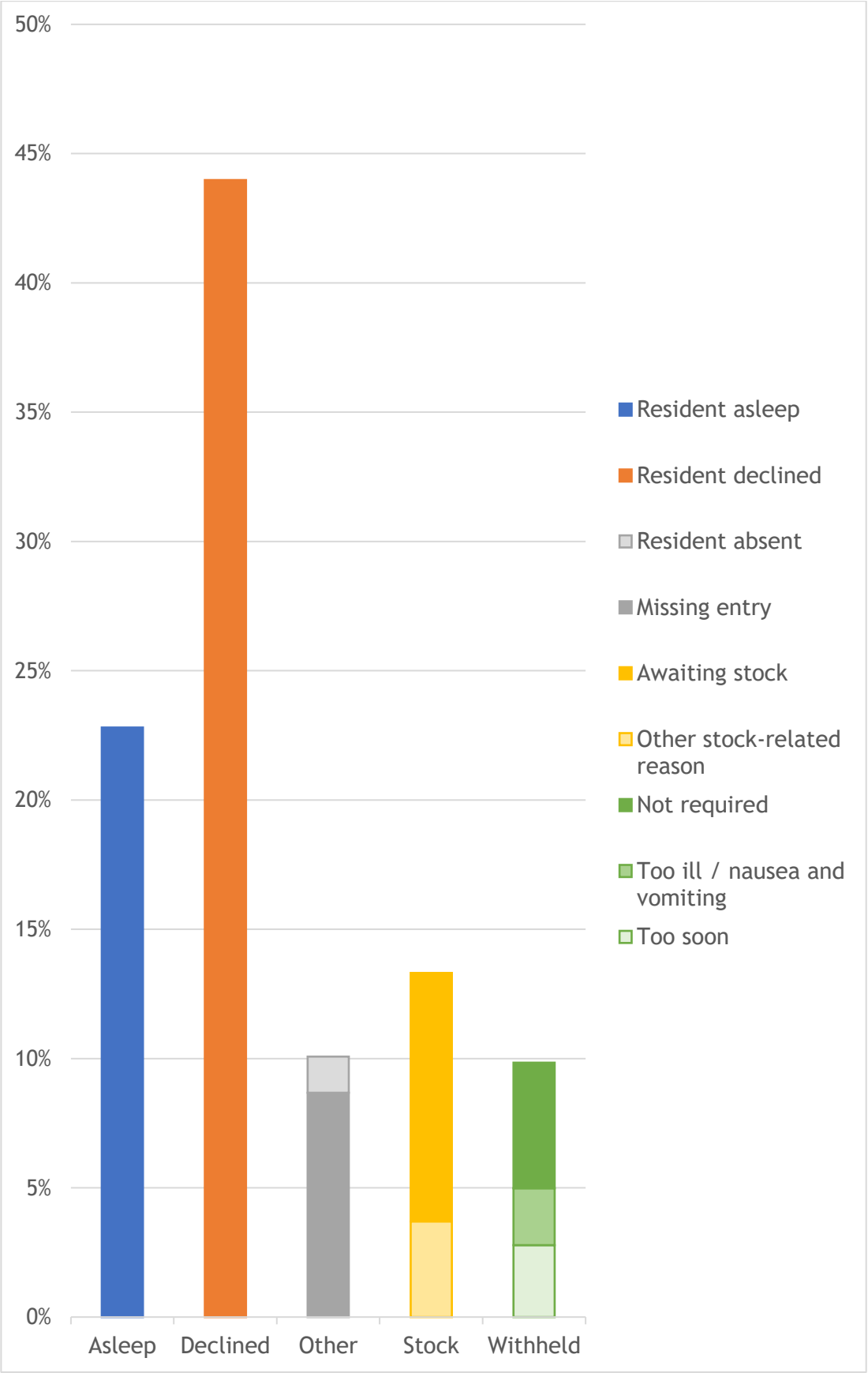

Figure 4.2: Reasons for dose omissions as a percentage of total omissions

4.5 DISCUSSION

This chapter has explored the prevalence of, and reasons for dose omissions of dopaminergic medicines in the care home setting, and is to the authors knowledge, the first research to evaluate this. Overall, 2.15% of doses were omitted, as measured by the total opportunities for error. This is lower than previous studies of PD medicines in hospital inpatients, for which estimates identified have ranged from 2.8% to 20% (Skelly et al. 2014; Martinez-Ramirez et al. 2015; Lertxundi et al. 2017; Hunt et al. 2018) (Derry et al. 2010; Hou et al. 2012; Nageshwaran et al. 2013). It is also lower than the prevalence rates reported for dose omissions across all medicines in the care home setting, which range from 3.6 – 7% (Barker et al. 2002; Alldred et al. 2009; Barber et al. 2009; Garratt et al. 2020). Reasons for this may include a greater focus on ensuring PD medicines are administered within the care home setting due to an awareness of the potential consequences of dose omissions, as well as fewer acute changes to health condition and a lower likelihood of being unable to take oral medicines, which is a common cause for dose omissions in the acute setting (Derry et al. 2010; Skelly et al. 2014; Skelly et al. 2017).

It should be noted that individuals in this analysis were included only where they had been a resident within the home for at least 28 days prior to the start of the study period. This was to enable the capture of typical day-to-day administration patterns, and to reduce the risk of inaccurate data near the time of admission (see Chapter Two). As previous research has identified greater odds of omissions of medicines within the first week following admission to a care home (Lane et al. 2014), it is probable that the results of this analysis underestimate the prevalence of PD dose omissions for new residents, who may be more likely to experience omissions, for example due to lack of medicine availability. Further research is needed to explore this.

This analysis found that, on the whole, the individuals studied had their dopaminergic medicines consistently administered, with 90% having fewer than 5% of doses omitted. This suggests there is greater adherence than in the community setting, for which studies have reported 15.3% taking fewer than 80% of doses and 12.5-20% of individuals taking less than 80% of their

total required dopaminergic medicine dose (Leopold et al. 2004; Grosset et al. 2005; Grosset et al. 2009). Around 3% of individuals had less than 80% of doses administered in this study. Further research is needed to assess this as a proportion of the total levodopa equivalent dose (LED) and to explore the clinical consequence of such omissions. However, this highlights the potential benefit of using eMAR data to find such 'needles in the haystack', which may benefit greatly from clinical review. The potential implementation of such approaches should be further evaluated for feasibility and acceptability.

4.5.1 Reasons for dose omissions

In this analysis, the majority of dose omissions were recorded to be a result of the individual declining to take their medicine (44%). This is higher than reported in the acute setting as proportion of all dose omissions (between 4 and 10% (Derry et al. 2010; Skelly et al. 2014)), but similar to the prevalence by total opportunities for error (0.95% compared to between 1.3 and 2.2% (Skelly et al. 2014)). Furthermore, similar results have been found in a study of dose omissions for all medicine classes in care homes (3.59% of doses omitted, of which 34.6% where a result of the resident declining the dose (Garratt et al. 2020)). Further research is needed to examine the reason for individuals declining doses and the approaches taken within the care home setting for managing this, particularly where they are frequent.

The second most common reason for omission was 'resident asleep', accounting for over a fifth of all omissions. This suggests a possible lack of awareness of the potential consequences of dose omissions for PD medicines. This highlights the potential benefit of wide-scale implementation of eMAR and subsequent harnessing of the data for the monitoring of service delivery, for example by regulatory bodies or Clinical Commissioning Groups and should be explored further. For such cases where evidence of a possible knowledge-gap is identified, an approach could be to develop an educational programme for staff, which could be delivered alongside support and monitoring for improvement.

Around 13% of dose omissions were a result of stock issues, including lack of medicine availability. This is similar to findings for PD medicines in the hospital setting (Derry et al. 2010; Hunt et al. 2018). However, as the eMAR system from which the data used in the analysis presented in this chapter provides automated assistance with stock management, for example through stock level alerts, it can be hypothesised that the results presented here may underestimate the prevalence of dose omissions as a result of stock unavailability in care homes. It should be noted that, although outside the scope of this thesis, where an eMAR data is linked to the dispensing pharmacy this also provides the opportunity for examination of the pharmacy supply chain. This may prove beneficial in root-cause analysis where dose omissions occur due to the absence of stock and should be explored in future research.

A very low proportion of doses were found to be withheld in this analysis, with these accounting for around 10% of omissions. Although this is lower than findings of previous research examining all medicines within the care home setting (Garratt et al. 2020), this can be considered expected due to the nature of the medicines studied in this chapter. While guidelines advise avoiding abrupt withdrawal of PD dopaminergic medicines, which should not typically be withheld without consultation with a PD specialist (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b), care home staff may be able to exercise their clinical judgment more frequently for other medicines used in the care home setting, temporarily withholding these while seeking further clinical input as needed, particularly in the nursing home setting.

Around a half of withheld doses were recorded as ‘not required’, and as no further details were available, it was not possible to determine whether there was reasonable justification for these doses being withheld, and/or any necessary advice was sought. Further research should examine whether this is recorded in the care plan. Meanwhile, almost 30% of withheld doses were because the attempt was ‘too soon’. However, as only one administration attempt was recorded for each resident – medicine – date required – time required combination for the dopaminergic medicines examined, no evidence could be found for these being later re-attempted. A

possible explanation could be where a previous dose was administered significantly late for medicines requiring frequent administration and, as such, the subsequent dose was due around the same time the dose should have been administered. Further research is needed to explore this hypothesis.

At 1.4% of the total, a low proportion of dose omissions were recorded as 'resident absent'. However, it is likely that a significant proportion of these would have been administered, with this recorded elsewhere. Similarly, around 9% of dose omissions in the analysis presented in this chapter were a result of missing entries. These represent a failure of staff within the care home to account for the dose in question (whether it is administered or not). Therefore, these doses may have been administered, with the staff member failing to record this. As a result, dose omissions in the 'other' category may not represent dose omissions and, with exclusion of these, the true prevalence of omissions of dopaminergic medicines may be as low as 1.93% in this study population. Further research is needed to examine the proportion of doses truly omitted in these cases, for example through discussion with residents and staff and/or analysis or care plan notes.

4.5.2 Levodopa vs other dopaminergic medicines

As in the hospital setting, a higher proportion of levodopa doses were omitted than other dopaminergic medicines (Martinez-Ramirez et al. 2015), however this was not found to be statistically significant. This may be a result of inadequate statistical power, with a much greater number of doses recorded for levodopa medicines compared to other dopaminergic medicines (36,603 vs 3,584), coupled with low rates of dose omission. Despite this, a significant difference in the number of individuals experiencing one or more dose omissions for levodopa medicines and other dopaminergic medicines was found (40% vs 20%, respectively, P=0.001). It can be hypothesised that such disparity may be a result of dose fractionation of levodopa regimens. As discussed in Chapter Three, the frequency of administration required for levodopa is typically higher than that required for other dopaminergic medicines. This therefore provides greater opportunity for error. More frequent administration may also be associated with lower adherence, as

seen in the community setting (Grosset et al. 2009) and may be more challenging for staff to manage alongside other duties; this should be explored in future research.

4.5.3 Limitations

Although it may be hypothesised that frequent dose omissions of dopaminergic medicines may lead to worsening of symptoms, the clinical effect where these were identified was not assessed in this study. Further research should be conducted to examine this. This could, in part, be undertaken with the use of medicines as proxy measures, for example laxatives use as a proxy for constipation, analgesics use as a proxy for pain, and antipsychotic medicine use as a proxy for psychotic symptoms. However, the use of eMAR data alone may prove ineffective in capturing a full picture of the clinical effect of such omissions and may miss factors such as mobility, the ability to perform activities of daily living, and quality of life. Therefore, a mixed methodology approach for such research should be considered, including qualitative research exploring resident and care home staff experiences, alongside quantitative analysis to explore the effects of dose omissions. The study of clinical outcomes may also be facilitated by the linkage of eMAR to electronic care plan records, which outline the residents physical and mental state throughout the day, alongside the care provided. The feasibility of such an approach should be explored.

The analysis presented in this chapter measures dose omissions as a proportion of total doses required. This is the measure recommended by the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence 2018). However, it is probable that dose omissions would have a greater impact on symptom control where a higher levodopa equivalent dose (LED) is required. A statistically significant positive association between the number of doses and the total levodopa LED administered has previously been reported (Nyholm and Stepien 2014), therefore the results for dose omissions as a percentage of the total LED would be expected to be similar to those found as a proportion of the total doses required. Despite this, future work should compare the strength of

association with clinical outcomes for these two methodologies of measuring dose omissions.

4.6 CONCLUSION

Although dose omissions for PD dopaminergic medicines were found to be less prevalent in the established care home population compared to hospital inpatients, there remains opportunity to reduce this form of MAE, particularly for the minority of individuals found to be experiencing very high levels of dose omissions. This highlights a potential benefit of using eMAR data for wide-scale monitoring, to help find these 'needles in the haystack'. In addition, further research examining individual and care home level factors contributing to, and outcomes associated with PD dopaminergic medicine dose omissions in such cases is needed, which may be facilitated by the linkage of eMAR and electronic care plan data.

5 TIMING OF LEVODOPA ADMINISTRATION

5.1 INTRODUCTION

As discussed in Chapter Three, maintaining a consistent schedule of administration for levodopa is important, particularly later in the course of Parkinson's disease (PD) as a shorter dose-response develops and the clinical effect of levodopa more closely mimics levodopa concentrations (Ahlskog 2014). As levodopa is used to help control the symptoms of PD, delays in administration can lead to worsening of symptoms (Pahwa and Lyons 2009), affecting quality of life and functional performance, which may not return to baseline on re-establishment of the individuals normal administration pattern (Parkinson's UK 2019). Meanwhile, shortening of the time between doses may increase levodopa concentrations, increasing the risk of peak-dose dyskinesias (Pandey and Srivanitchapoom 2017).

The importance of the timing of levodopa administration is reflected in clinical guidance and reports. A National Patient Safety Agency (NPSA) alert in 2010 highlighted the need to reduce harms for hospitalised individuals occurring as a result of omissions or delays of medicines (Rehman 2010). This included PD medicines, for which they stated a dose given 2 hours outside of the prescribed time had the potential to have a significant or catastrophic long-term impact (Rehman 2010). Meanwhile, Parkinson's UK's 'Get it on time' campaign report "calls on all UK hospitals and care homes to ensure every person with Parkinson's receives their medication on time, every time" (Parkinson's UK 2019). Finally, Statement 4 of the National Institute for Health and Care Excellence (NICE) Quality Standard for PD (QS164), states that "Adults with Parkinson's in a hospital or care home should receive their Levodopa within 30 min of its prescribed time" (National Institute for Health and Care Excellence 2018).

5.1.1 Levodopa timing in the hospital setting

Historically, there has been significantly more attention on the timing of levodopa administration within the hospital setting compared to the care home setting, although this is still limited and largely based on survey data (Gerlach et al. 2012; Parkinson's UK 2019). These include surveys of healthcare professionals, which suggest there is little confidence that PD medicine doses are consistently administered on time in hospitals. For example, 61% of respondents to a survey of UK consultant geriatricians, consultant neurologists, and nurse specialists involved in the management of PD reported a lack of confidence that PD medications were administered on time (Skelly et al. 2015). Meanwhile, in a survey of healthcare professionals working in Centres of Excellence and Care Consortium Centres in the US and internationally, only 6% of centres said they were either confident or very confident that PD patients received their medicines on time (Chou et al. 2011). However, it should be noted that these surveys did not explicitly state what should be considered 'on time' by participants.

These findings are supported by the results of a survey of individuals with PD and their carers reported by Parkinson's UK, which found that, when admitted to hospital, over half of individuals had received their PD medication at the wrong time, and a further 14% had received these on time but reminding healthcare staff had been required (Parkinson's UK 2019). Almost 80% of individuals given their PD medication at the wrong time reported a worsening in their condition as a result, with over a third stating their PD was considerably worse (Parkinson's UK 2019). Factors considered to be associated with mistiming of medication included under-staffing, inadequate staff training, failure to assess for or allow self- or unpaid carer administration, and restriction of patient access to their PD medicines (Parkinson's UK 2019). Furthermore, as outlined in Chapter Four, the 'Get it on Time' report also highlighted that data on the quality of administration of PD medication was frequently not available for monitoring purposes. As a result, the report recommended delays of more than 30 minutes should be recorded as patient safety incidents (Parkinson's UK 2019).

A similar prevalence of mistiming has been seen in a small pilot study examining the effect of a specialist PD unit on medicine prescribing and administration in admissions of individuals with PD to an English hospital over a 3-month period (Skelly et al. 2014). This found 66% of levodopa doses were administered on time in the specialist PD unit compared to 48% on general wards (Skelly et al. 2014). For the doses that were not administered on time, 10% were administered early and 24% and 42% were administered late on the PD unit and general wards, respectively (Skelly et al. 2014). However, this study only examined 44 participants (Skelly et al. 2014).

Internationally, a lower prevalence of PD medicine administration mistiming has been reported. For example, in a Dutch study, a quarter of the 123 survey respondents who had been hospitalised in the previous year reported having experienced errors in the administration of their PD medicines during admission, with around 80% of these due to mistiming (Gerlach et al. 2012). In this study, almost half of admissions to the neurological wards were a result of medicine issues (Gerlach et al. 2012). Furthermore, incorrect medicine administration was found to be associated with increased odds of deterioration of PD (odds ratio 5.8), which was statistically significant even after adjustment of multiple factors, including levodopa equivalent dose (LED), PD duration and severity, and consultation with a PD nurse specialist (Gerlach et al. 2012). 44% of the individuals who experienced such a deterioration during admission reported that a full return to baseline functioning had not been made following discharge i.e. their deterioration was pervasive (Gerlach et al. 2012).

Interestingly, a review of the clinical notes of approximately half of the participants in this study found that motor symptom deterioration and medicine issues were recorded less frequently than reported in the survey (Gerlach et al. 2012). It is unclear if this is a result of over-reporting in the survey or under-reporting in the clinical notes. However, as only one individual had motor symptom decline recorded in their clinical notes, it can be suggested this is more likely to be a result of under-reporting in clinical notes (Gerlach et al. 2012). Alongside failed recognition, other hypothetical causes of this could include time pressures of staff, or differences in what is

considered a clinically significant decline in motor function or clinically significant alteration in medicine administration regimen by healthcare professionals compared to individuals with PD.

5.1.2 Levodopa timing in the care home setting

Social care regulations mandate that the date and either exact time, or time of day, at which medication administration attempts take place are recorded (Care Quality Commission 2021b). With paper MAR charts, this requirement is often met through recording the timing of the medication administration round, for example 'Morning', 'Lunch', 'Evening' or 'Night' (Al-Hamadani 2018). This limits the ability to retrospectively analyse the accuracy of timing of administrations and may in part explain the paucity of research into the timing of administration of PD medicines within care homes i.e. the data simply is not available via paper-based MAR charts.

Whilst no care home based studies examining the timing of PD medicine administrations could be found, it can be hypothesised that mistiming may be prevalent as care homes experience many of the same issues as hospitals, including a high number of staff vacancies (Hunt et al. 2020), which has been found to be associated with a lower level of care quality (Allan and Vadean 2021). Furthermore, residential homes rely on care staff alone, who may have no previous knowledge or specific training on PD and the importance of medicine timing for dopaminergic medicines. Ensuring staff are sufficiently trained and knowledgeable is likely to be challenging given the high rate of staff turnover in many care homes which has been estimated to be over 20% per annum (Costello et al. 2020). The characteristics of PD medicine regimens may also increase the risk of mistiming of administration, as the high frequency of administration required for some PD patients due to fractionation of dosing (Brooks 2008; Nyholm and Stepien 2014) may mean the scheduled timing of administration(s) falls outside the four traditional care home medicine rounds (Alldred et al. 2009, p. 19; Al-Hamadani 2018, p. 19; Parkinson's UK 2019).

5.2 AIM

This aim of this chapter is to explore the timing of administration of levodopa medicines, examining the following at both administration and individual level:

1. The prevalence of mistimed administration of levodopa doses
2. The concordance between the time prescribed and the time administered (Dosing Accuracy), and the difference between the observed and expected gap between doses administered (Dosing Precision)

5.3 METHODOLOGY

This chapter explores the timing of regular levodopa medicines recorded in the core dataset that were administered during the study period. The PD table was used as the base for this. For more details on the creation of the core dataset see Chapter Two, and for details on the PD table see Chapter 3.3.3.4 Estimation of required daily levodopa equivalent dose (LED). Data was extracted using SQL Server Management Studio (SSMS) v18 (Microsoft 2019).

5.3.1 Measurements of timing

Two measures of levodopa timing were considered 1) dosing accuracy and 2) dosing precision. Dosing accuracy was defined as the difference between the date and time a dose was required, as scheduled on the device, and the date and time the dose was administered. This is the approach recommended by the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence 2018). Dosing precision was measured as the difference between the observed gap and the expected gap between administration attempts. The expected gap was computed as the difference between the last required date and time a dose was administered and the required date and time of administration for the current dose, while the observed gap was calculated as the difference between the date and time the last dose was administered and the date and time the current dose was administered.

Measurements were computed to the nearest minute. A measure of 0 was recorded where there was no difference between the required time and the administered time (dosing accuracy) or no difference between the expected gap and the observed gap between administrations (dosing precision); a measurement of more than 0 where the administered time was after the required time (dosing accuracy) or the observed gap between dose administrations was longer than the expected gap (dosing precision); and a measurement of less than 0 where the administered time was before the required time (dosing accuracy) or the observed gap between dose administrations was shorter than the expected gap (dosing precision). In accordance with the NICE Parkinson's disease Quality Standard (QS164) Quality statement 4, doses were considered 'on time' if they were between -30 minutes and 30 minutes, inclusive, 'early' when less than -30 minutes, and 'late' when more than 30 minutes (National Institute for Health and Care Excellence 2018).

To facilitate the calculation of the measures used in the timing analysis, fields returning the 1) last date and time a dose was required, 2) the last date and time a dose was administered, and 3) the last required date and time at which a dose was administered were added to the PD table. The PD table was then filtered on administrations where 1) the current dose was administered, 2) the Levodopa LED was >0 (levodopa-containing medicine) and 3) the previous dose was administered (identified by the last date and time the dose was required being equal to the last required date and time at which a dose was administered. Only administrations where the previous dose was also given were examined to enable a clearer comparison of measurements of dosing accuracy and dosing precision, as dosing precision would include the time during which levodopa was omitted in the measurement. In clinical practice, it would be probable that the proportion of dose omissions and the proportion of doses not administered 'on time' would be presented together. Therefore, inclusion of the omitted time in the dose precision measurement would potentially result in the number of doses affected by either dose omissions or mistiming being overstated.

5.3.2 Administration-level comparison of measures

Values returned at administration level for dosing accuracy and dosing precision were extracted from SQL and exported to Microsoft Excel 365 (Microsoft [no date]). The distribution of these were visualised in Microsoft Excel and using Q-Q plots produced with R v3.6.1 (RStudio 2021; R Core Team 2019). Due to the presence of both skew and heteroskedasticity, a modified Bland-Altman plot (Bland and Altman 1999), employing 0.025, 0.5 and 0.975 quantile regression lines was used to assess for agreement between the two measures. A similar approach has been applied in previous research (Eisinger-Watzl et al. 2015). This was produced in R v3.6.1 (RStudio 2021; R Core Team 2019) using the quantreg package v5.85 (Koenker 2021). Test for statistical significance between the measurements of dose accuracy and dose precision at administration level is not reported, as multiple administrations were included from each individual and medicine at different points in time. Therefore, observations fail the assumption of independence (Schober et al. 2018).

5.3.2.1 Identification of doses as 'early', 'late' or 'on time'

Doses were categorised as either 'early', 'late' or 'on time' in Microsoft Excel 365 (Microsoft [no date]), as previously defined in part 5.3.1, and a contingency table constructed. Sensitivity, specificity and positive and negative predictive values were calculated for the ability of dosing accuracy to identify variations in the gap between doses (dosing precision), and McNemar test, conducted in R v3.6.1 (RStudio 2021; R Core Team 2019), was used to assess for a statistically significant difference in the categorical measurements results seen for measurements of dosing accuracy and dosing precision.

5.3.3 Resident-level comparison of measures

For each resident, the percentage of doses administered 'on time' were calculated in SQL for both measures using a common table expression (CTE[12]). This produced a table returning the results of measures for dosing

[12] A common table expression (CTE) in SQL allows a temporary table of results to be produced, which can be used in subsequent queries Microsoft. 2017d. *WITH common_table_expression (Transact SQL)*. Microsoft. Available at:

accuracy and dosing precision, alongside flags to identify where these were ‘on time’ (between -30 and 30 minutes, inclusive). This was used to compute the number of doses administered ‘on time’, the number of doses mistimed, the total doses administered, and the percentage of doses administered ‘on time’ (total doses administered ‘on time’ divided by the total doses), grouped by Resident ID.

The results were exported to Microsoft Excel 365 (Microsoft [no date]), in which a scattergraph was plotted to view the association between the percentage of doses identified as administered ‘on time’ by the measure of dosing accuracy compared to dosing precision. Due to the presence of skew, Spearman’s Rho was used to assess for a statistically significant correlation between the two measures and, as with the administration-level comparison, a modified Bland-Altman plot (Bland and Altman 1999), with 0.025, 0.5 and 0.975 quantile regression lines, was used to assess for agreement. Both were conducted in R v3.6.1 (RStudio 2021; R Core Team 2019), with the quantreg package used to produce quantile regression lines (Koenker 2021).

5.4 RESULTS

5.4.1 Administration-level comparison of measures

A total of 35,279 medicine administrations were identified for regular levodopa medicines during the study period. The mean values returned for dosing accuracy and dosing precision for these were 31.66 and 0.01, respectively. A different distribution was seen for the timings produced by measurement of dosing accuracy and dosing precision (Figure 5.1). While the distribution seen for dosing precision was symmetrical around 0 (median 0 minutes, interquartile range -24 to 24 minutes), a right skew was seen for dosing accuracy (median 22 minutes, interquartile range 6 to 52 minutes). Q-Q plots showed divergence from the normal distribution, with evidence of right skew for dosing accuracy (Figure 5.2) and over-dispersion for dosing precision (Figure 5.3).

https://docs.microsoft.com/en-us/sql/t-sql/queries/with-common-table-expression-transact-sql?view=sql-server-ver15 [Accessed: 23/09/2021]. .

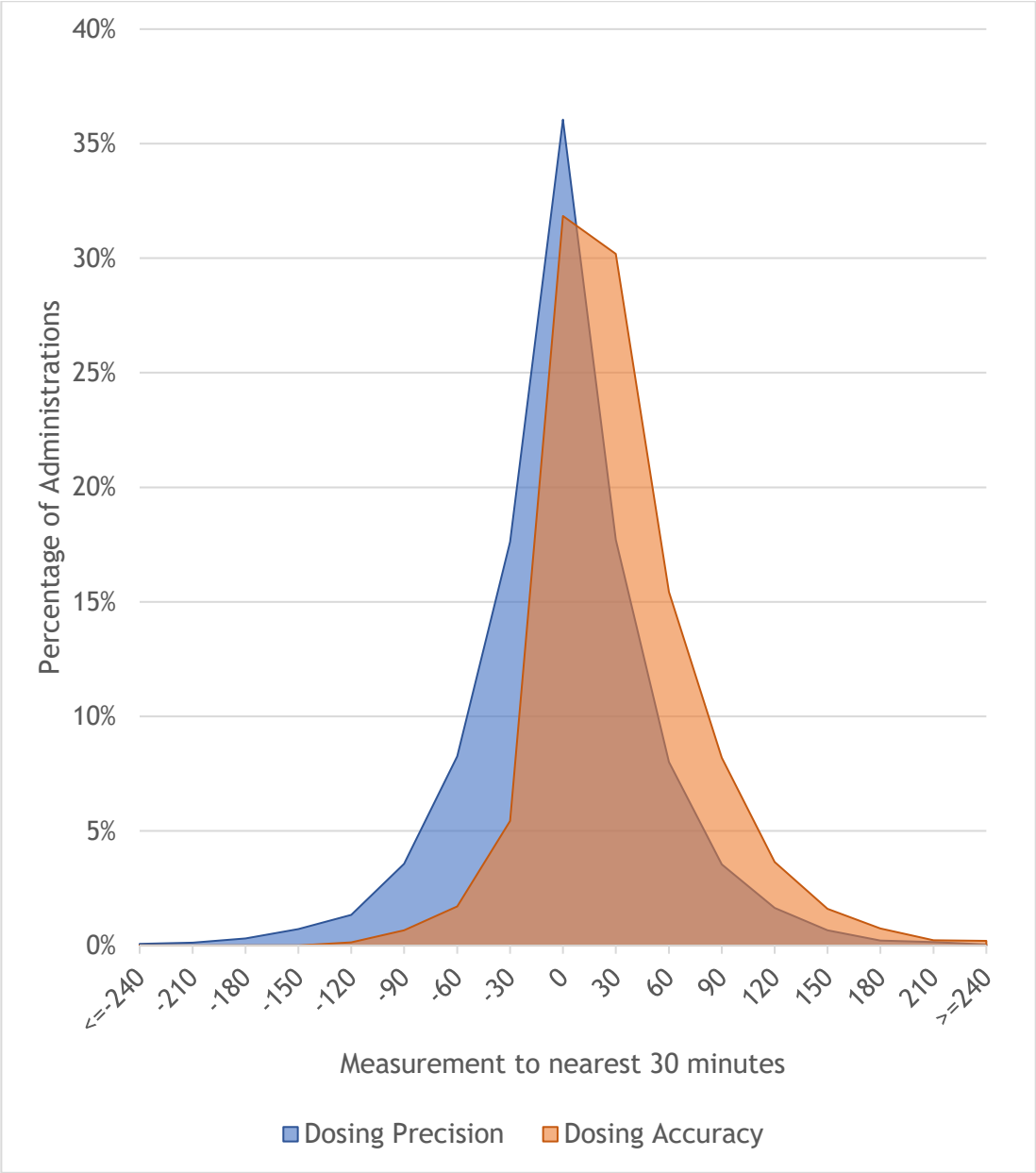

Figure 5.1: Percentage of administrations for each measurement to the nearest 30 minutes for dosing precision and dosing accuracy

Most doses were administered within 90 minutes of the required time (90.11%). However, a large degree of spread was seen at extremes, with around 4% of doses recorded as administered more than two hours after the required time, and 32 doses (0.09%) recorded as administered 4 or more hours after the required time (dose accuracy >= 240 minutes). Meanwhile, 13 doses (0.04%) were recorded with an observed gap four or more hours less than the expected gap since the previous dose (dosing precision <= 240 minutes).

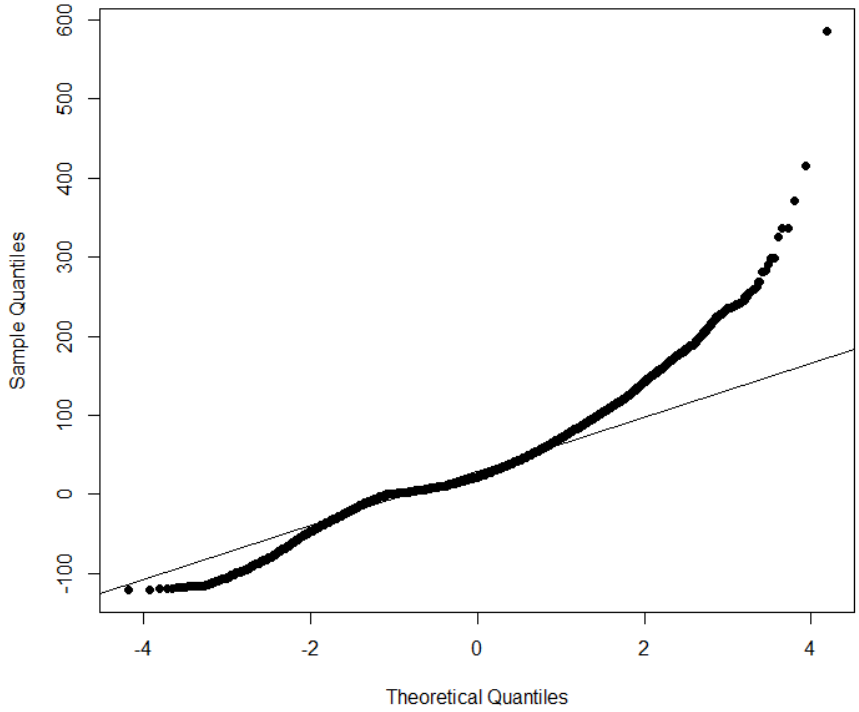

Figure 5.2: Q-Q plot for dosing accuracy

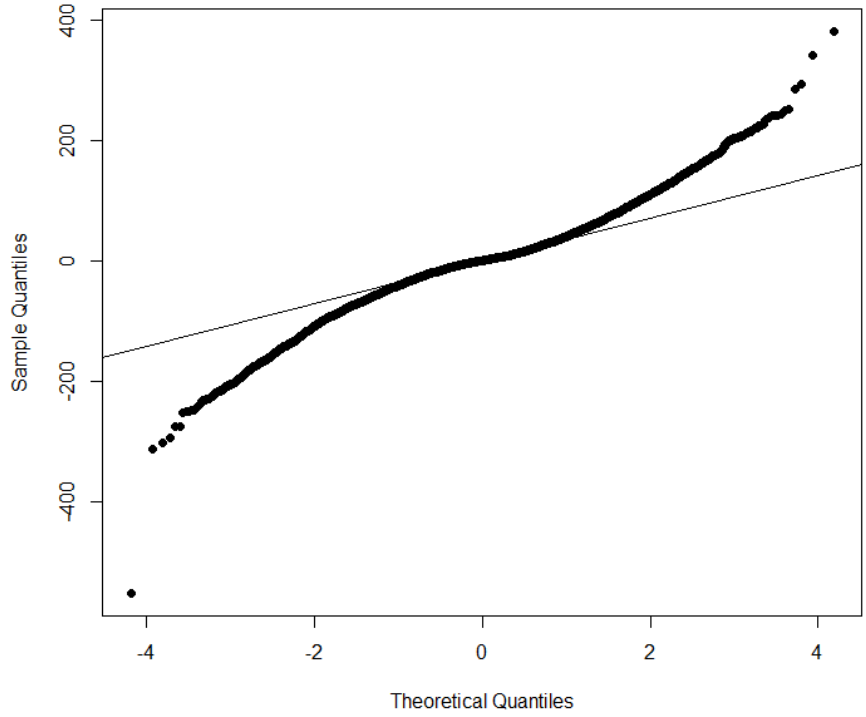

Figure 5.3: Q-Q plot for dosing precision

Like the raw values for dosing accuracy and dosing precision, the mean and difference between the two measures were not normally distributed (Figures 5.5 and 5.6). Therefore, a percentile Bland-Altman plot was used in place of Limits of Agreement based on mean and standard error. Examining this plot in Figure 5.4, there are a large number of points above and below the 97.5% and 2.5% estimated percentile lines, respectively, with several extreme upper values where the measure of dosing accuracy was much greater than dosing precision. Furthermore, where the average between dosing accuracy and dosing precision was negative, the 2.5% line is seen to be closer to zero on the y-axis (indicating no difference) than the median line.

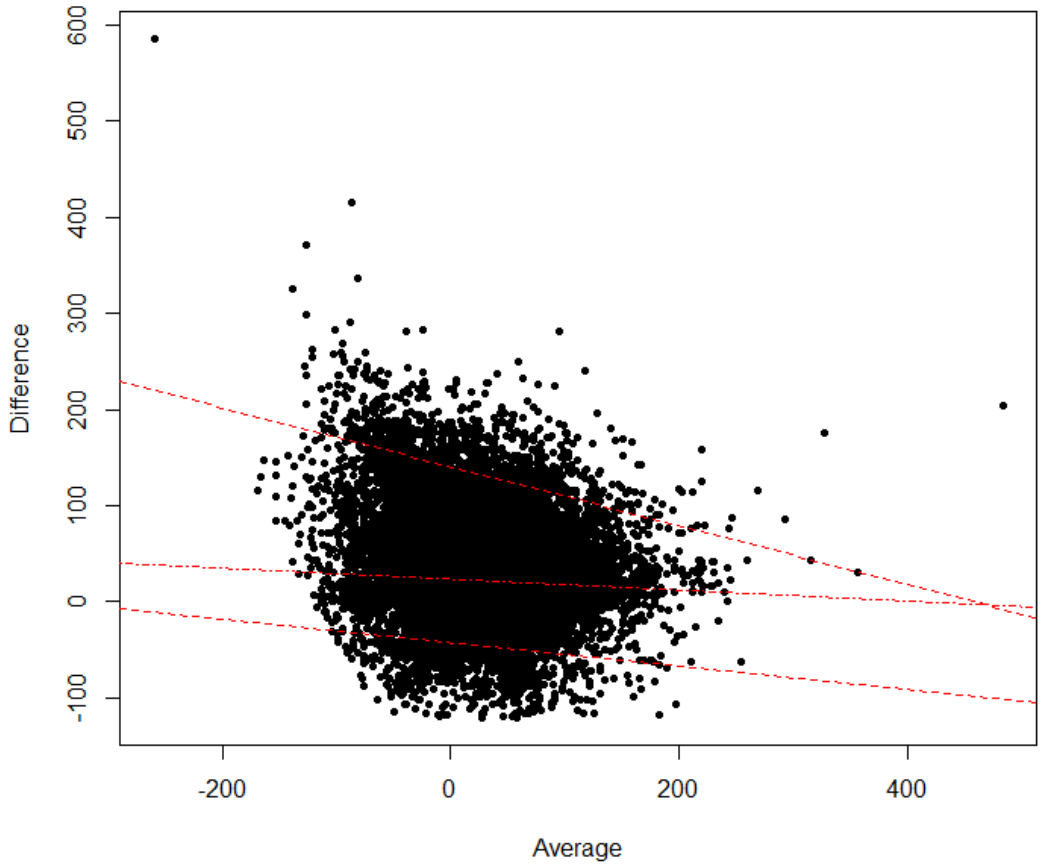

Figure 5.4: Comparison of measured times for dosing accuracy and dosing precision at administration level, using a Bland-Altman plot with 2.5, 50 and 97.5 percentile lines, computed using quantile regression

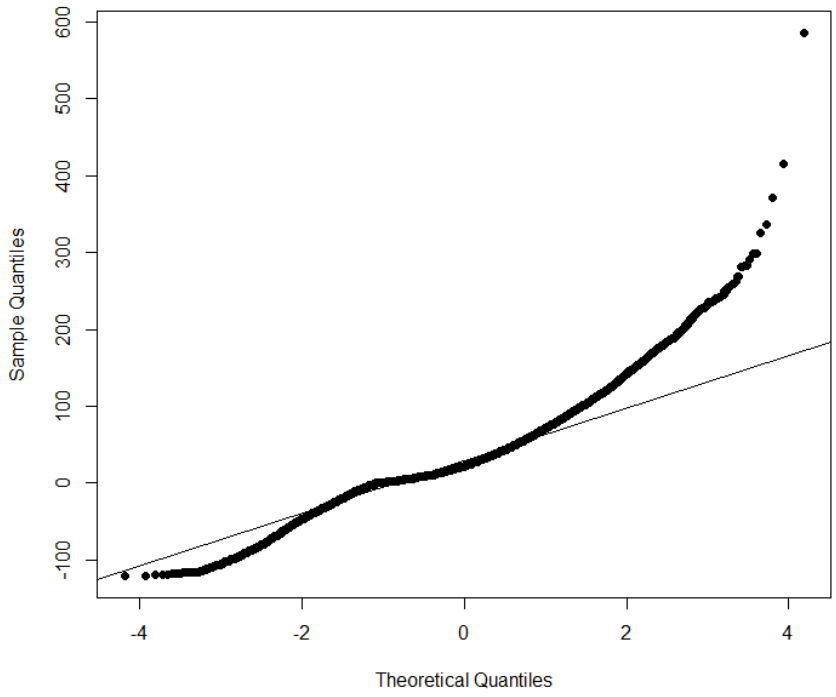

Figure 5.5: Q-Q plot for the difference between dosing accuracy and dosing precision

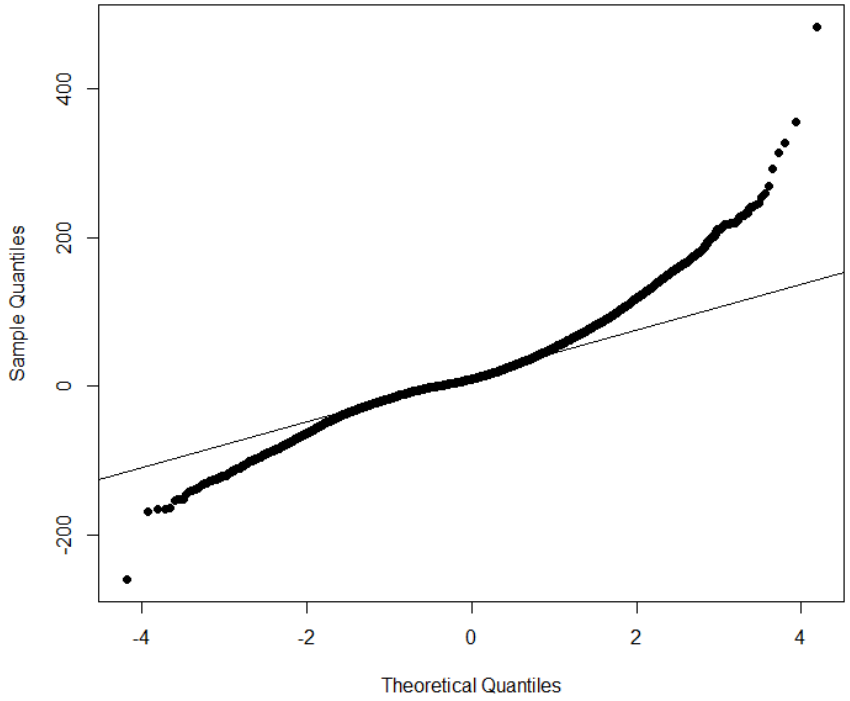

Figure 5.6: Q-Q plot for the average between dosing accuracy and dosing precision

5.4.1.1 Identification of doses as 'early', 'late' or 'on time'

Figure 5.7 shows the proportion of doses administered 'early', 'late' and 'on time', as identified using measures of dosing accuracy and dosing precision, respectively. For both measures, over a half of doses were administered 'on time' (54% and 58%, respectively). However, while the same proportion of doses were administered either 'early' or 'late' as measured by dosing precision (21%), the measure of dosing accuracy identified a greater proportion of doses to be administered 'late' (42% compared to 4% administered 'early').

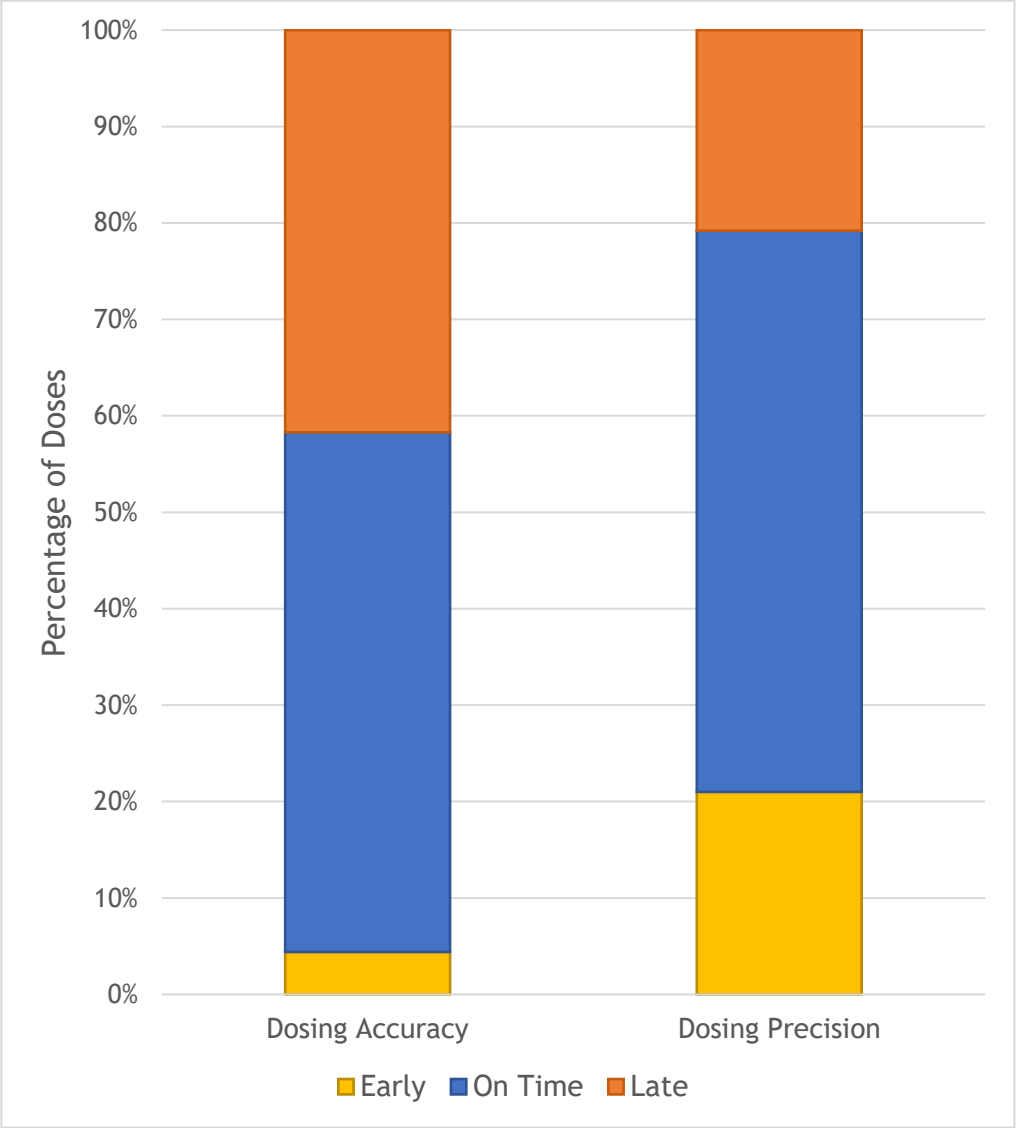

Figure 5.7: Percentage of doses identified as 'early', 'late' and 'on time' for dosing accuracy and dosing precision

As shown in contingency Table 5.1, measures of dosing accuracy and dosing precision were in agreement for around 60% of doses and 38% of doses were identified as being 'on time' by both measures. Where measurements were not in concordance, dosing accuracy more commonly identified doses as 'late' (58% vs 7%), while dosing precision more commonly identified doses as 'early' (44% vs 3%). The difference in the categorical measurement results seen for dosing accuracy and dosing precision were found to be statistically significant (P<0.001).

Overall, dosing accuracy showed only moderate sensitivity and specificity for identifying a dosing precision of between -30 and 30 minutes, inclusive (62.60% and 65.71%, respectively), with a slightly higher negative value (NPV) compared to positive predictive value (PPV) (71.00% and 56.73%, respectively). A higher sensitivity was seen for the detection of 'late' doses compared to 'early' doses (85.80% and 14.36%, respectively), while a higher PPV was seen for 'early' doses (68.29% vs 42.79%).

Table 5.1: Contingency table showing the number of administration (% of grand total) measured to be early, late and on time, for dosing accuracy and dosing precision

		Dosing Accuracy			
		Early	On Time	Late	Total
Dosing Precision	Early	1,064 (3.02)	4,519 (12.81)	1,826 (5.18)	7,409 (21.00)
	On Time	448 (1.27)	13,493 (38.25)	6,592 (18.69)	20,533 (58.20)
	Late	46 (0.13)	996 (2.82)	6,295 (17.84)	7,337 (20.80)
	Total	1,558 (4.42)	19,008 (53.88)	14,713 (41.70)	35,279 (100.00)

5.4.2 Resident-level comparison of measures

A total of 319 individuals were using regular levodopa medicines. As shown in Figure 5.8, a sizable proportion of doses were not administered within 30 minutes of the required time for the majority of individuals, with a median of 50.91% of doses administered within 30 minutes of the required time (i.e. dosing accuracy 'on time') (interquartile range 29.51% to 71.43%). While a fairly even distribution in the percentage of doses administered 'on time' was seen for dosing accuracy, symmetry was seen around 40 to 50% of administrations for dosing precision, with a smaller proportion of individuals identified at both extremes for this measure (Figure 5.9).

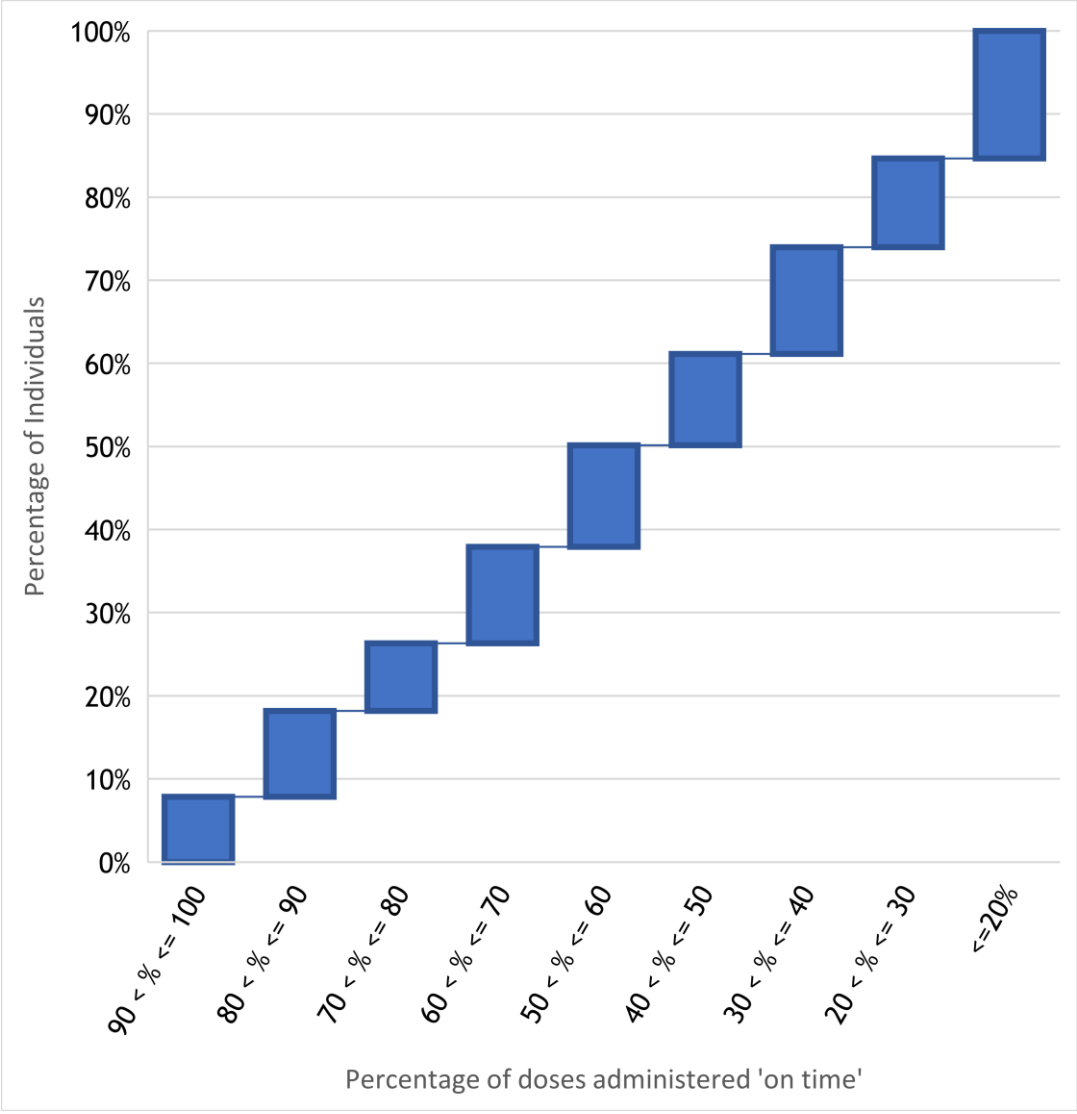

Figure 5.8: Visualisation showing the breakdown of the percentage of doses administered 'on time' per resident for dosing accuracy

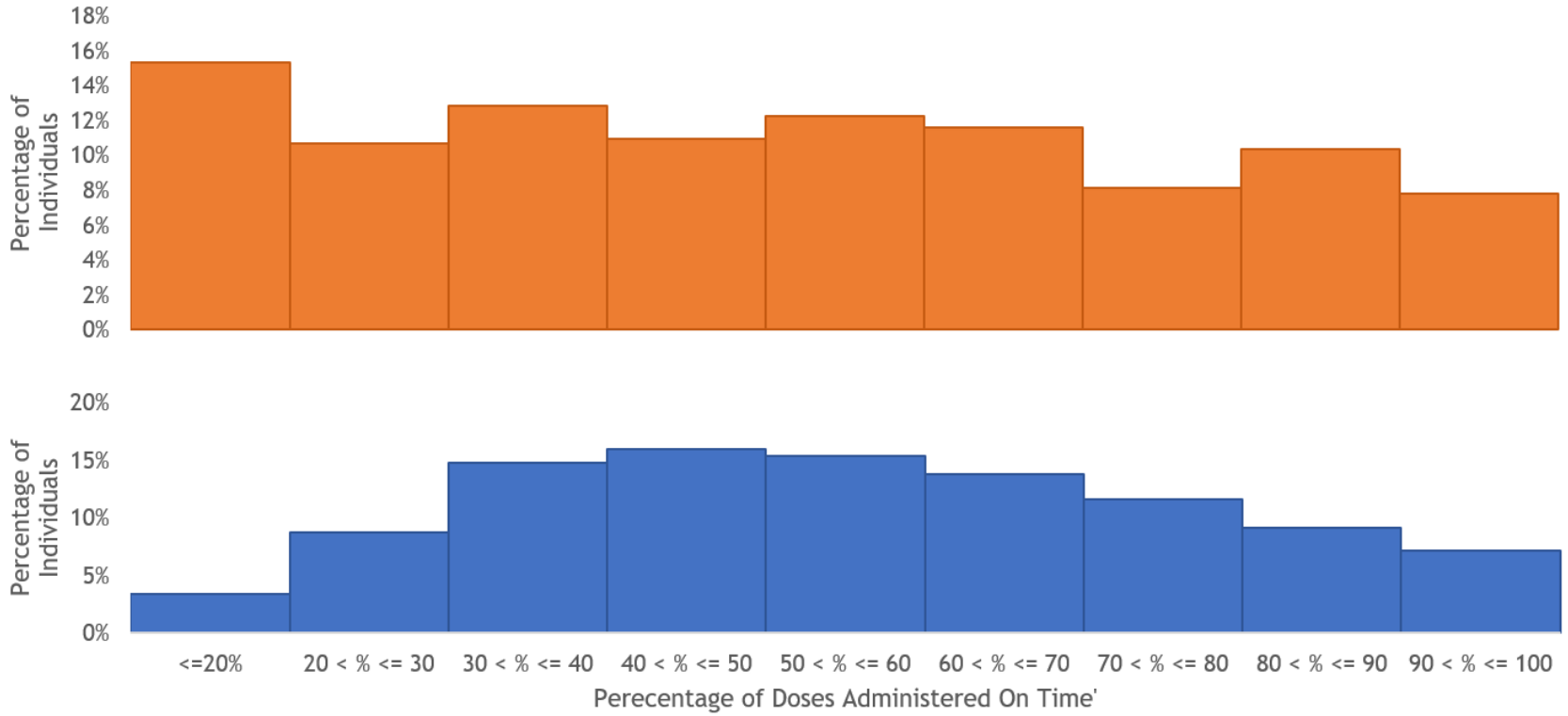

Figure 5.9: Percentage of doses administered 'On Time' as measured by Dosing Accuracy (top) and Dosing Precision (bottom)

As seen in Figure 5.10, as moderate positive correlation was seen between the percentage of doses measured as ‘on time’ by dosing precision and dosing accuracy. This was found to be statistically significant (0.580, P<0.001). However, a large degree of variability was seen, particularly where a low percentage of doses were identified as administered ‘on time’ by one of the measurements. Furthermore, only 12 of the 319 individuals had the same percentage of doses identified as administered ‘on time’ by both measures.

Figure 5.10: Scattergraph showing the correlation between the percentage of doses identified as 'on time' by measurement using dosing accuracy vs dosing precision

The mean and difference between the percentage of doses identified as administered ‘on time’ by the two measures were not normally distributed (Figures 5.12 and 5.13). Therefore, quantile regression was used to produce the percentile Bland-Altman plot in Figure 5.11. This shows a funnel shape, with substantial heteroskedasticity for individuals with a lower average percentage of doses administered. As such, the Limits of Agreement (LOA) identified by quantile regression for a 95% prediction interval are broader on the left. Furthermore, the median line shows a slight positive trend, and does not follow zero on the y-axis, suggesting systematic and proportional errors are also present.

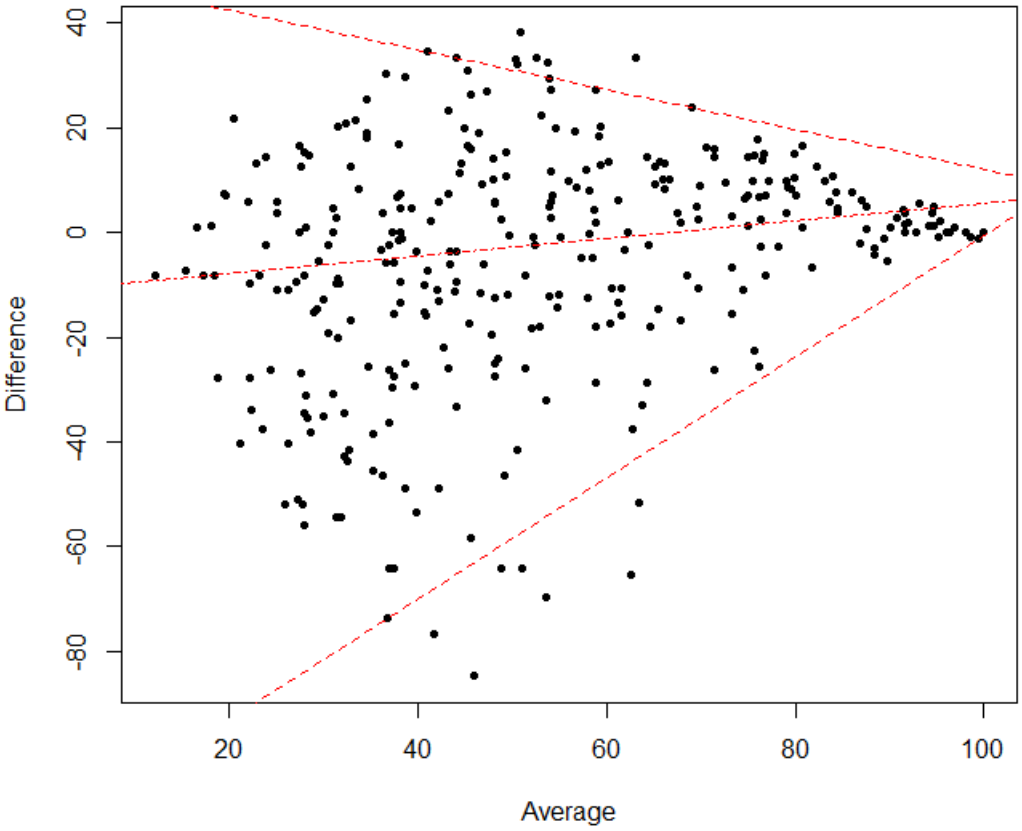

Figure 5.11: Comparison of the percentage of doses identified as ‘on time’ by measurement using dosing accuracy vs dosing precision at individual level, using a Bland-Altman plot with 2.5, 50 and 97.5 percentile lines computed using quantile regression

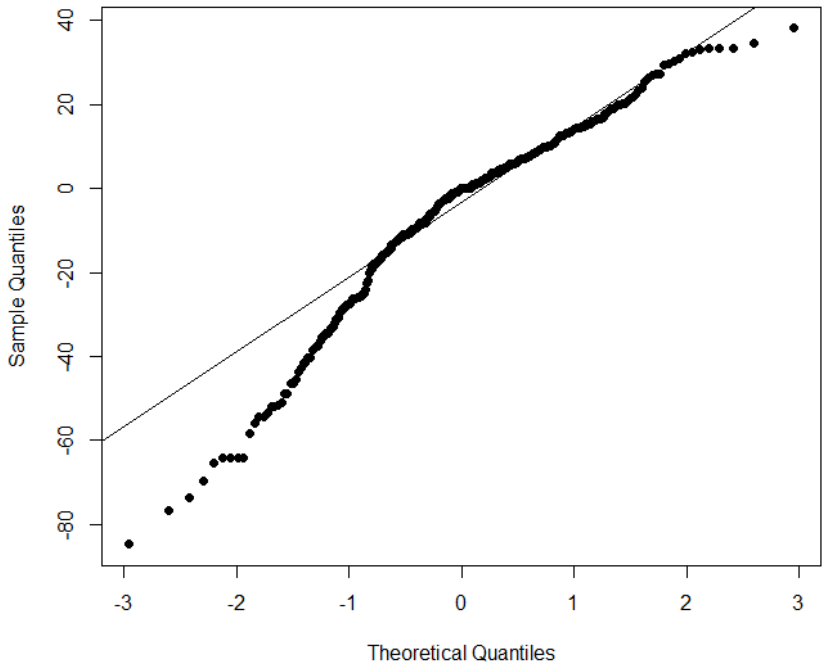

Figure 5.12: Q-Q plot for the difference between the percentage of doses identified as 'on time' by dosing accuracy and dosing precision

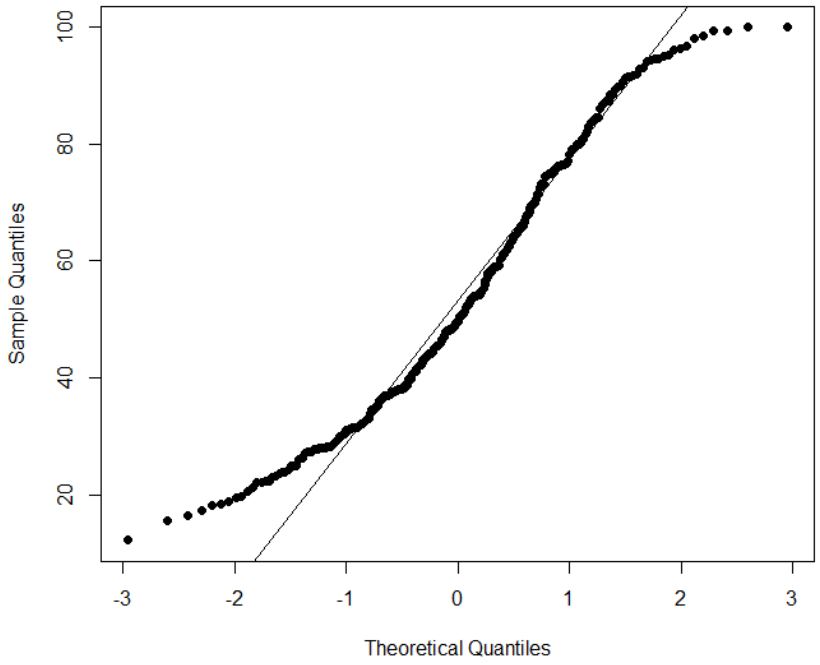

Figure 5.13: Q-Q plot for the average of the percentage of doses identified as 'on time' by dosing accuracy and dosing precision

5.5 DISCUSSION

As outlined in the introduction, medicine administration issues such as omissions and mistiming have been found to be associated with an increased risk of worsening of motor symptom in individuals during a hospital admission (Gerlach et al. 2012; Parkinson's UK 2019), which appears to be pervasive for a significant proportion of individuals (Gerlach et al. 2012). Therefore, as it can be hypothesised that similar outcomes would be seen in the care home setting, maintaining a consistent medicine administration pattern for levodopa can be considered an important aspect of optimising functioning and quality of life in these residents.

The results found in this chapter suggest that mistimed administration of levodopa is common in the care home setting, with almost half of all doses administered either 'early' or 'late'. This is similar to findings in the hospital setting (Skelly et al. 2014). A larger proportion of doses were identified as administered more than 30 minutes after the prescribed time (i.e. late) than more than 30 minutes before the prescribed time (i.e. early) (42% vs 4%). This may be due to systems at the care home which remind staff that an administration is due at the prescribed time, making early administration less likely. Furthermore, warnings displayed by the electronic medicine administration record (eMAR) device when an administration is attempted prior to the scheduled time may dissuade staff from early administration, as these would need to be manually overridden. However, another factor could be time pressures experienced by care staff, and therefore it is notable that a similar split in 'early' and 'late' administrations has been seen in the hospital setting (10% of doses administered early vs 24-42% of doses administered late) (Skelly et al. 2014).

Over a fifth of doses were administered more than one hour after the required time, and around 4% more than two hours after the required time. Such long delays have been noted to have the potential for significant or catastrophic long-term impact in the hospital setting (Rehman 2010). Of particular concern was the finding that some doses were administered very late, with 32 doses (0.09%) recorded as administered more than 4 hours after the required time. Identification of such extreme values may enable more

prudent prioritisation of individuals and care homes for review by healthcare professionals such as pharmacists and PD nurse specialists.

Although measures of dosing accuracy and dosing precision identified a similar number of doses to be 'on time', dosing accuracy identified a greater proportion of doses as 'late', with a right skew in distribution seen compared to the symmetrical distribution of dosing precision. The symmetry around 0 minutes seen for dosing precision is to be expected, as without an even weighting between the number of minutes administered 'early' and the number of minutes administered 'late' for this measure, the time each dose is given would need to get increasingly later or earlier every day over the study period. Given the limited number of doses administered before the required time, the doses identified as 'early' by the measure of dosing precision are likely to be a result of time being 'caught up' from a previous late dose.

Little agreement was seen between measures of dosing accuracy and dosing precision at administration level, with a large number of points outside the 95% prediction range of the Bland Altman plot. Furthermore, the 2.5% percentile line was closer to zero on the y-axis than the median line for negative average values. Given that, where the average of the two measures were negative, the mean measurements for dosing accuracy and dosing precision were -0.66 and -44.28, respectively, this suggests dosing accuracy may underestimate any shortening between doses. However, it should be noted that this may have been skewed by an outlier in the upper right, for which a difference in measurements of almost 10 hours was found.

The tendency for dosing accuracy to overestimate dosing precision is supported by a median difference (dosing accuracy – dosing precision) of 22 minutes across all administrations. This suggests that the difference between the prescribed time and the administered time may not be a reliable measure for capturing fluctuations in dopaminergic levels as a result of mistimed administration. Similarly, statistically significant discordance was found between the identification of doses as 'early', 'late' or 'on time' between the two measures (McNemar $P<0.001$), with a particularly low sensitivity for

'early' doses (14%). This is notable as a shortening of the gap between doses may result in a higher than expected levodopa concentration, and therefore a greater risk of adverse effects such as peak-dose dyskinesias (Pandey and Srivanitchapoom 2017).

The prevalence of mistiming at individual level was found to be higher than survey results in the hospital setting (Gerlach et al. 2012; Parkinson's UK 2019), with most individuals affected. A possible reason for this may be that the length of stay in hospital was shorter than the 28-day period used in this thesis, resulting in fewer doses administered, and thus a reduced opportunity for mistimed administrations to occur. Furthermore, these studies are based on retrospective surveys, and so are likely to be subject to recall bias (Gerlach et al. 2012; Parkinson's UK 2019).

On average, each individual in this analysis had around a half of all doses administered 'on time'. However, considerable variability was seen, with interquartile ranges of 30-71% and 39-73% for dosing accuracy and dosing precision, respectively. This suggests that mistiming of levodopa is a relatively frequent occurrence, which affects a large proportion of doses for most individuals. As in the assessment at administration level, little concordance was seen between the percentage of doses identified as being administered 'on time' at individual level for the two methods of measurement, with especially high variability seen where a low proportion of doses were administered 'on time'. This suggests that these two measures should not be used interchangeably.

5.5.1 Implications for research and clinical practice

The rate of mistimed administration found in this study, as measured by the difference between the required time and the administered time, fell between the rates reported for general hospital wards and a PD Unit in a previous study of PD medicine timing during admission to an English hospital (Skelly et al. 2014). The authors of this study found significantly fewer omissions and a greater proportion of doses were administered on time within the PD Unit, with 66% of levodopa doses administered on time in the PD Unit compared to 48% on general wards (Skelly et al. 2014). Similar

clustering of individuals with PD into dedicated nursing homes has been considered as a means of improving the management of PD in previous research (van Rumund et al. 2014). However, concerns have been raised by individuals with PD, their caregivers and healthcare professionals, including increased distance from home reducing the ability of friends and family visiting, the high physical and mental demand that would be required of staff working in specialised care homes and the emotional and psychological burden of witnessing the effects of PD in other individuals with later stage PD (van Rumund et al. 2014).

The findings of poor levels of agreement between the measures of dosing accuracy and dosing precision presented in this Chapter raises questions over the suitability of the use of the difference between the prescribed time and the administered time for measuring the timing of PD medicine administration. The findings of this analysis suggests that dosing accuracy may not accurately capture the concertina effect of lengthening and shortening of the expected gap between doses of levodopa at individual or administration level. This has implications for both research and healthcare purposes. For example, the use of the difference between the prescribed time and the administered time in research exploring the association between the timing of levodopa administration and clinical outcomes such as motor symptoms, quality of life and hospital length of stay may be subject to Type II errors, as this may not capture fluctuations in levodopa concentrations due to variations in the gap between doses.

Furthermore, in individuals where a larger proportion of doses were identified as being administered ‘on time’ by the dosing accuracy measurement compared to the dosing precision measurement, this can be hypothesised to be a result of required administration times being met for some doses but missed for others, whereas a larger proportion of doses identified as being administered ‘on time’ by the dosing precision compared to the dosing accuracy can be hypothesised to be the result of a full shift in administration times, such that all doses are consistently administered either ‘early’ or ‘late’. Therefore, different approaches to managing these within the healthcare setting may need to be employed. For example, in cases

where all doses are consistently administered later than the required time, such that the actual gap between doses remains similar to the prescribed gap between doses, it may be suitable to amend the times for scheduled administration to reflect this. Indeed, consistent late administrations are unlikely to lead to fluctuations in motor symptoms where the gaps between administrations remains as scheduled. Therefore, a change in medicine regimen may be appropriate for any uncontrolled motor symptoms. However, in cases where a large fluctuation is seen in the gaps between doses, a more appropriate approach for uncontrolled motor symptoms may be an initial review featuring: i) analysis to determine if this coincides with fluctuating gaps between doses; ii) an exploration of reasons for mistiming of administration within the care home; iii) remedying the mistimings and iv) a period of symptom monitoring following correct timing of administration.

The findings of this chapter suggest that mistiming of levodopa is common in the care home setting, and that eMAR data may be useful for identifying and monitoring this. This is particularly the case where the aim is to identify lengthening and shortening in the prescribed gap between doses as even if recording of the exact time of administration was enforced, this would be extremely complex and time-consuming to analyse with paper MAR charts. Therefore, the use of eMAR data should be considered for healthcare monitoring and the development of complex intervention protocols for motor symptom management using PD medicine regimens. This should follow guidance for the development of complex interventions (O'Cathain et al. 2019). First, evaluation of the clinical effectiveness of precise levodopa timing on motor symptom control in the care home setting is needed, along with the reasoning for mistimed administration. An exploration of technical, financial and workforce feasibility should also be conducted, in addition to qualitative research involving individuals with PD, and a range of health and social care professionals, including PD specialists to explore the acceptability of proposed interventions. Finally, any agreed interventions should be piloted before wide-scale implementation, examining whether the desired outcomes are achieved, and whether any unforeseen harms are uncovered (O'Cathain et al. 2019).

5.5.2 Limitations

In addition to those mentioned in previous chapters, a limitation of this study is the potential for administration to have been retrospectively recorded at the care home, affecting estimates of timing of administration based. This may lead to an overestimation in the measurements of levodopa timing. However, as the CQC require care homes to complete medication records as soon as possible after administration, it is likely that this would affect a minority of records (Care Quality Commission 2021b). In addition, as individuals who are self-administering medications may not be added to the eMAR device at the care home, the results of this chapter cannot be considered representative of this group.

5.6 Conclusion

Mistiming of administration of levodopa was found to be common in the care home setting and affected most individuals. Little concordance was seen between measures of dosing accuracy and dosing precision, suggesting that the difference between the prescribed time and the administered time may not be an effective proxy for capturing lengthening and shortening in the gap between doses. Monitoring of the timing of levodopa administration and the development of complex interventions to improve this may be beneficial in the PD care home population. However, further research is needed to evaluate the reasons for mistimed administrations, and to explore the benefits of precise timing of levodopa administration in the care home population to verify this.

6 GENERAL DISCUSSION

The aim of this thesis was to explore the potential utility of medicines related data captured via an electronic medicines administration record (eMAR) system for research and clinical practice. The research focussed on the long-term, older adult care home population in England and used Parkinson's disease (PD) as a case study. The research presented involved the secondary analysis of pseudonymised eMAR data, provided under a data sharing agreement from a commercial partner.

6.1 Summary of findings

6.1.1 Chapter Two: Core Dataset Creation

Chapter Two focussed on the creation of a core dataset from the 'raw' database. This core dataset was then used as the foundation for the subsequent studies. As this thesis presents a secondary analysis of routinely collected data, data pre-processing was required to produce a core study dataset for the purposes of this piece of work. This included imputation of data fields where a variable of interest was not directly provided (i.e. the calculation of age from the year of birth, and the use of Title as a proxy for sex). In addition, inclusion and exclusion criteria were applied to the raw dataset. These criteria had two purposes. Firstly, it addressed potential data quality issues in the original dataset (e.g. medicines not being marked as stopped when an individual was no longer residing at the care home). Secondly, it facilitated the creation of a homogenised sample of older adult, long-stay care home residents in England. This could then be compared to national datasets, including the Care Quality Commission (CQC) Directory of services (Care Quality Commission 2021a), and Office for National Statistics (ONS) census data (Office for National Statistics 2003,2013) to explore representativeness.

The majority of exclusions of individuals were the result of the individual being marked as 'archived', and therefore no longer resided at the care home (86.25%). Exclusion for this reason was necessary as the dataset did not include a field indicating when an individual was archived, and around a half of all residents marked as archived still had one or more medicine recorded as active. This suggested that the presence of active medicines in

any resident record could not reliably be used as a proxy for current residence at the care home. Other potential data quality issues identified included a small proportion of entries with a year of birth of 1900. This would mean the individual was 120 years old. As 01/01/1900 is the default value for date fields in SQL, a failure to record these residents' date of birth on the eMAR device at the care home can be considered a more likely reason for a year of birth of 1900, with a date of birth of 01/01/1900 recorded by default in the blank field. Exclusion of individuals for this reason resulted in the removal of 203 of the 37,258 individuals within the raw dataset.

Examination of demographic factors of cases within the core dataset found a low level of representation of care homes. An estimated mean of 2.81% of care homes were represented in each postcode area. Despite this, the core dataset spanned a wide range of postcode areas in England, with a moderate, statistically significant correlation found between the number of care homes within the CQC Directory (Care Quality Commission 2021a) and the number of care homes in the core dataset per postcode area ($P<0.001$). This suggested that the core dataset may be a fairly representative with respect to regional spread. Conversely, the number of individuals included per care home in the core dataset was significantly lower than the number of registered beds per care home recorded in the CQC Directory (medians 27 vs 35, $P<0.001$) (Care Quality Commission 2021a). This may be, at least in part, due to other exclusion criteria applied in the formation of the core dataset e.g. age, active medicines use), coupled with a proportion of registered beds being unused (estimated to be around 10% in previous research (Brame et al. 2019)). However, a statistically significant difference in distribution remained after adjustment for a 90% estimated occupancy rate (medians 27 and 32, $P<0.001$). Finally, examination of age and sex found a continuation of trend towards an older aged care home population, with an increasing male proportion sex in comparison to ONS census data from 2001 (Office for National Statistics 2003) and 2011 (Office for National Statistics 2013).

In conclusion, Chapter Two formed a core dataset in a cleaned state for further analysis. This was felt to be moderately representative of the broader care home population for variables of geographical distribution, age and sex.

6.1.2 Chapter Three: Parkinson's Disease (PD)

Chapter Three examined the PD sub-population within the core dataset, using the prescribing of dopaminergic medicines as a proxy for a clinical diagnosis. The prevalence of PD within the core dataset was identified to be around 4%, which is higher than seen in the general population (up to around 2%, dependent on age and sex) (Wickremaratchi et al. 2009; 2017; Doyle 2018), but within the range seen in previous studies examining the care home population (1.6 to 6.8%) (Larsen 1991; Mitchell et al. 1996a; Lapane et al. 1999; Porter et al. 2010). Individuals identified with PD were dispersed across many care homes, with around 60% of care homes providing services to one or more of these individuals. Individuals in the study dataset were more likely to be younger and male where they were identified as a PD resident (mean age 83 vs 86; 45% and 29% male, respectively; $P<0.001$). However, individuals with PD in care homes appear to be older than those living in the community (Hand et al. 2016), with a greater female proportion (Lapane et al. 1999; Buchanan et al. 2002; Weerkamp et al. 2012; Walker et al. 2014; McLean et al. 2017; Weir et al. 2018).

Almost all dopaminergic medicines were recorded as regular scheduled medicines (96.5%) (i.e. not for use 'as required') and most individuals were prescribed levodopa (90%); this is similar to findings in work examining residents of Dutch nursing homes (Weerkamp et al. 2012). However, as in previous research (Hand et al. 2016), lower use of other dopaminergic medicines was seen compared to estimates for use in the community setting (Nyholm and Stepien 2014; Hand et al. 2016). For example, 14% of individuals in this analysis were using a dopamine agonist compared to 39-65% in the community (Nyholm and Stepien 2014; Hand et al. 2016). Finally, a lower average frequency of administration and daily levodopa equivalent dose (LED) was found in this analysis than previous research examining this in the community setting (Damier et al. 2008; Grosset et al. 2009; Nyholm and Stepien 2014) (Hutton et al. 1988; Hutton and Morris 1991) (Sivertsen et al. 1989) (Hand et al. 2016) (Walker et al. 2014) (Weerkamp et al. 2012). This may be due to increased susceptibility to adverse effects of dopaminergic

medicines (Kadastik-Eerme et al. 2017) or undertreatment (Weerkamp et al. 2012), and should be explored further.

6.1.3 Chapter Four: Dose Omissions of Dopaminergic Medicines

Chapter Four examined the prevalence of, and reasons for dose omissions of regular dopaminergic medicines. Reassuringly, only around 2% of doses were omitted and the majority of individuals (~60%) received all scheduled doses. This represents a lower rate of dose omissions compared to the acute setting for dopaminergic medicines (2.8% to 20%) (Skelly et al. 2014; Martinez-Ramirez et al. 2015; Lertxundi et al. 2017; Hunt et al. 2018) (Derry et al. 2010; Hou et al. 2012; Nageshwaran et al. 2013). Similarly, the prevalence of dose omissions was lower than reported across all medicine classes within the care home setting (3.6% to 7%) (Barker et al. 2002; Alldred et al. ; Barber et al. 2009; Garratt et al. 2020). This suggests that care home staff may take greater care in avoiding dose omissions for PD medicines due to an awareness of the potential consequences of omitting these medicines. Of note, individuals were more likely to experience a dose omission of levodopa during the study period compared to other dopaminergic medicines (40% vs 20% P=0.001). This may be due to a higher frequency of administration for levodopa, which may be challenging for staff to manage alongside other duties.

The most common reason recorded for dose omissions was the resident declining (44% of dose omissions, 0.95% of all doses), followed by the resident being asleep (23% of dose omissions, 0.49% of all doses). The recording of the resident being asleep as a reason for not administering dopaminergic medicines is an interesting finding, as this suggests a possible lack of awareness of the importance of avoiding omissions of PD medicines by the staff administering these doses. This should be explored further and the development and implementation of an educational programme in such cases should be considered. Meanwhile, 13.3% of dose omissions (0.29% of all doses) were due to stock issues, which is similar to findings in the hospital setting (Derry et al. 2010; Hunt et al. 2018).

Guidance cautions against withholding PD medicines without specialist advice (British National Formulary [no date]a; National Institute for Health and Care Excellence 2017b). Therefore, this may explain the lower proportion of doses recorded as withheld compared to previous findings across all medicine classes in the care home setting (9.8% vs 15.5%) (Garratt et al. 2020). Finally, missing entries were recorded for 0.19% of all doses, suggesting either a failure of attempting to administer, or a failure of accounting for the result of the dose. Although a low proportion, maintaining complete and accurate medicine records is important as failure to do so may lead to harm e.g. through accidental double-administration of a dose.

6.1.4 Chapter Five: Timing of Levodopa Administration

Chapter Five examined the timing of levodopa administration using two measures 1) dosing accuracy – the time between the date and time the dose was required and the date and time the dose was given and 2) dosing precision – the time between the date and time a dose was given and the date and time at which the previous dose was given. Current guidance on the audit of the timing of levodopa recommends doses should be administered 'on time' with no more than a 30-minute gap between the date and time a dose is prescribed and the date and time at which a dose is administered (National Institute for Health and Care Excellence 2018). However, no previous research benchmarking or auditing this target in the care home setting could be identified.

The analysis in Chapter Five found that only around 54% of doses were administered 'on time', with a median dosing accuracy measurement of 22 minutes (interquartile range 6 - 52). This equates to the average dose being administered 22 minutes after the required time. Almost all individuals had a dose administered either early (i.e. more than 30 minutes before the prescribed time) or late (i.e. more than 30 minutes after the prescribed time). Of note, only 8% of individuals received over 90% of doses 'on time'. Furthermore, little agreement was seen between measures of dosing accuracy and dosing precision, suggesting that measuring the difference between the time prescribed and the time administered may not fully capture the true variations in time between doses as a concertina effect can

emerge. As a short duration of the clinical effect of levodopa is often seen in individuals later in the course of PD (Ahlskog 2014), such fluctuations may be associated with poorer control of symptoms and reduced motor function. Further research is needed to examine this.

6.2 LIMITATIONS

The main aim of this thesis is to consider the potential for the use of eMAR data in future research and clinical practice through exploration of a novel database. As a result, an exploratory and data-driven design was implemented. This involved examining the database to assess its feasibility for use in uncovering different types of medicine use patterns, which were taken forward for further analysis. This approach has the potential to introduce bias. Another limitation is the evaluation of multiple hypotheses using the same data source. This is associated with an increased risk of occurrence of Type 1 errors, as the probability of returning a statistically significant result is higher across all tests than for each test individually. Therefore, in light of these limitations, replication is necessary, and results should be interpreted cautiously. Nevertheless, it is notable that, where inferential tests returned very low P-values, these would remain statistically significant with Bonferroni correction.

Due to the secondary nature of this work, analyses were constrained by the availability of data. For example, no information was provided for the type of care home (i.e. nursing or residential), Care Quality Commission (CQC) inspection ratings, or resident ethnicity. These are factors that are likely to impact upon health status and quality of care. For some factors that were absent, this was partly addressed through the computation of new data fields using those available (e.g. sex using Title; age using Year of Birth; quantity administered using changes in stock levels). However, these may be subject to error. For example, an individual's Title may not reflect their biological sex. Meanwhile, estimation of the quantity required for administration for regular medicines using the modal change in stock level, while reducing the impact of stock changes unrelated to medicines administration (e.g. receipt

of stock from dispensing pharmacy; manual adjustments following a stock-take), may miss adjustments to the required dose during the study period.

Where examining the PD sub-population, a significant limitation was the absence of clinical details to allow for the confirmation of diagnosis or therapeutic indication for medicines use. Although the use of medicines as a proxy for PD is an approach that has been used in previous research (Parsons et al. 2012), this may mistakenly include some individuals using dopaminergic medicines for other indications (British National Formulary [no date]b; British National Formulary [no date]c; Harding and Cox 2015), while excluding individuals with PD not managed with medicines (estimated at around 5% (Walker et al. 2014)). Furthermore, while this thesis has examined for possible deviations from expected patterns of medicines use, assessments of whether such observations were appropriate (i.e. there was a good reason for deviations, such as following advice from a specialist), or the clinical outcomes resulting from this were not explored. As with confirmation of diagnosis and therapeutic indication, absence of information from either residents and staff at the care home or care planning notes acts as a constraint on the hypotheses that can be tested using eMAR data. In effect, it is challenging to determine the outcomes of deviations from expected medicines use patterns, for example for quality of life and mobility.

Despite attempts to clean the data through the formation of a core dataset, there remained some evidence of potential data quality issues, which emerged during the analysis. For example, 30 active regular dopaminergic medicines had no administrations scheduled throughout the entire study period. As attempts would be expected to be recorded in the eMAR database where required, even when not administered, this suggests that these individuals may have not been residing at the care home during the study period, either temporarily, or permanently with failure to record the individual as ‘archived’.

6.3 RECOMMENDATIONS

Through the exploration of medicines use in Parkinson's disease (PD), this thesis has demonstrated feasibility of the use of eMAR data for research and clinical practice to identify medicines use patterns that may lead to poor clinical effectiveness of medicines or potential harm. Specifically, the thesis has demonstrated utility in exploring medicines use at a scale not afforded by analysis of paper-based MAR chart records or observational studies that have been the mainstay for research in care homes. Despite the benefits of the approach, further work is needed to realise the full potential of eMAR data sources.

6.3.1 Research

As discussed in this thesis, access to pseudonymised eMAR records has the potential to facilitate large-scale research on medicines use in care homes. This has traditionally been challenging due to difficulties in obtaining data specific to this population. To overcome this, previous research has employed approaches such as the use of read codes number of individuals living in a postcode/address and other techniques to attempt to identify care home residents within primary care data (Shah et al. 2010; Shah et al. 2012). Such techniques need careful consideration of the criteria used to identify care homes. A balance must be struck between criteria that identify all individuals as care home residents and overidentification and/or contamination of a care home study population with individuals living in the community (Shah et al. 2010). The use of eMAR data provides a potential solution for this.

Moreover, while the use of primary care data with identification techniques has facilitated some large-scale research into medicines prescribing in the care home population (Shah et al. 2012), study of administration patterns has historically been more challenging due to the use of paper MAR charts. Generally, these are only accessible at the care home, and require a considerable amount of time and resource to analyse (Al-Hamadani 2018). Likely as a result, MAR chart analyses have been limited, both in number and in the size of data analysed. For example, one of the most well-known, breakthrough studies examining medicines use in care homes in the UK, the

Care Homes Use of Medicines study (CHUMS) provided research evidence on the prevalence of medicines administration errors (MAEs) (Alldred et al. ; Barber et al. 2009). However, the researchers used an observational approach, with only two medicine administration rounds observed for each resident (Alldred et al.). Notwithstanding the low sample number, the observational approach is subject to the Hawthorne effect, where participants may have 'reacted' to being observed and modified their behaviour (McCambridge et al. 2014). In contrast, the use of eMAR data in a similar study allowed partial replication of the study aims but with a much longer study duration of 3 months (Szczepura et al. 2011). Furthermore, eMAR data improves the feasibility of studying a large sample size of residents across many care homes. For example, in the core dataset produced in Chapter Two, 9,082 residents across 310 care homes were identified following the application of inclusion and exclusion criteria. This compares to 256 residents across 55 care homes in the CHUMS (Alldred et al.).

The ability to study individuals across a large number of care homes becomes increasingly beneficial as specific clinical conditions are being examined. This is demonstrated by the identification of a sub-population of individuals for the examination of Parkinson's disease (PD) using dopaminergic medicines as a proxy for identification, outlined in Chapter Three. This identified 375 individuals across 186 care homes and equates to approximately 2-3 residents with PD per care home. Therefore, if researchers were to use paper-based MAR charts to study this population, it would involve a significant travel burden between care homes to ensure a sufficient sample size was obtained.

Finally, as described in this thesis, eMAR records can provide more granular and precise data on medicines use, particularly with respect to the timing of medicines administration. This is information that is typically missing from paper MAR charts, with the time of the round (e.g. morning, lunch etc.) or the time required generally used in place of the actual time the medicine was given. Routine recording of the precise time an administration attempt has taken place using paper records, or the recording of this in observational

studies, would likely prove time-intensive and would remain less accurate than automated timestamping. Through the examination of the timing of administration of levodopa presented in Chapter Five, this thesis has shown that the use of eMAR data for examining the timing of administration is feasible. Further, with over 35,000 administrations examined in this analysis, this approach allows a large number of administration episodes to be examined, even at medicine level.

Despite this, the use of eMAR data as supplied for analysis in this thesis cannot adequately address all research questions. For example, the dataset does not feature diagnosis, symptomology, and functioning. Furthermore, it does not capture qualitative data on the resident, care home staff and healthcare professionals' perspectives on the reasoning for, and appropriateness of medicine use patterns seen. As a result, the author recommends eMAR data is used in tandem with other research methodologies, including qualitative studies. For example, an approach could be the use of eMAR data to explore the scale of possible medicine-related issues, supplemented with smaller scale, more detailed studies through research methods such as interviews, observational studies and randomised control trials.

6.3.2 Clinical application

In recent years, there has been a growing drive to look beyond medicines management (ensuring the correct processes are followed) to also ensure that medicine regimens are optimised. As described by NHS England, "medicines optimisation looks at the value which medicines deliver, making sure they are clinically-effective and cost-effective. It is about ensuring people get the right choice of medicines, at the right time, and are engaged in the process by their clinical team." (NHS England [no date]). The optimisation approach includes a reduction in overprescribing, with a recent report suggesting a 10% reduction in prescribed items may be possible (Department of Health and Social Care Medicines Directorate 2021). A common approach for medicines optimisation is introducing pharmacist-led medicines reviews. This has been trialled in the Medicines Optimisation in Care Homes (MOCH) project, a 2-year scheme that supported pharmacists to

undertake postgraduate training to become experts in medicines optimisation in the care home setting (Pharmacy Integration Fund 2018). The continuation of these specialist pharmacy roles has been supported in the NHS Long-Term Plan (Department of Health and Social Care Medicines Directorate 2021).

Examinations of the outcomes of pharmacist-led medicines reviews in care homes in Wigan Borough Clinical Commissioning Group (CCG) (Swift and Trumper 2017) and East Sussex CCG (Blythin 2019) have found a reduction in the average number of medicines prescribed by 1.5 and 2, respectively. Meanwhile, Somerset CCG found a mean of 2.3 interventions were made per resident reviewed by pharmacists between 2014 and 2019 (Alves et al. 2019). Although mixed results have been found for cost reduction, these have reported savings of up to around £250 (Department of Health and Social Care Medicines Directorate 2021) per resident reviewed (Zermansky et al. 2006; Blythin 2019) (Alves et al. 2019). Interventions made as a result of pharmacist-led reviews have been reported to reduce the risk of harm (Department of Health and Social Care Medicines Directorate 2021). For example, it has been estimated that 12-16% of interventions made for medicines use had the potential to impact patient safety (Alves et al. 2019; Blythin 2019). A statistically significant reduction of 38% for the number of falls has also been reported (Zermansky et al. 2006).

However, as data on the interventions made is often collected manually, it has been noted that detailed evaluation of the interventions made at medicine level is not always possible (Swift and Trumper 2017). Furthermore, reviews are often time-intensive, taking around 1-2 hours per review (Alves et al. 2019; Blythin 2019). This may explain the challenge in undertaking an annual review with all care home residents as recommended (National Institute for Health and Care Excellence 2015a; Care Quality Commission 2019). Previous research has found this target was met in approximately a quarter of care home residents studied (Zermansky et al. 2006), compared to 44% of individuals living in the community (Zermansky et al. 2001).

The MOCH programme overview, published in 2018, identified the need for pharmacy professionals to have adequate access to data to facilitate medicines optimisation, and thus listed the use of technology to support medicines optimisation programmes as an area of focus for evaluation (Pharmacy Integration Fund 2018). Allowing select healthcare professionals controlled, remote access, to eMAR data may enable wide scale monitoring, identification of cases of potentially inappropriate medicine use, and prioritisation of individuals for review. This may include, for example, the identification of individuals with frequent dose omissions of required medicines, (Chapter Four), or regular use of prescribed 'as required' medicines.

Previous research has identified the most common intervention made by pharmacists following review to be 'technical change' (30%), for example removing discontinued medicines and generic switching (where a medicine is switched for another version with the same active ingredient (Rathe et al. 2015)). Similarly, approximately 40% of individuals reviewed required a test for monitoring (Rathe et al. 2015). Applying machine learning to an eMAR dataset could allow for the development of automated processes for identifying such cases. This would enable practitioners to spend more time on person-centred and complex aspects of the review process rather than an initial triage of the data. Furthermore, the use of eMAR data could allow detailed, longitudinal evaluation of interventions made as a result of such reviews at medicine level, without increasing the administration burden for clinical staff.

A systematic review examining the use of computerised clinical decision support systems (CCDS [14]) in care homes suggested that, although implementation of such systems was currently low, the application of these systems may improve prescribing and reduce the risk of harm amongst residents (Marasinghe 2015). However, it is notable that very few primary

[14] Computerised clinical decision support systems (CCDSS) provide advice to healthcare professionals on potentially inappropriate medicines prescribing. Marasinghe, K. M. 2015. Computerised clinical decision support systems to improve medication safety in long-term care homes: A systematic review. *BMJ Open* 5(5), p. e006539. doi: http://dx.doi.org/10.1136/bmjopen-2014-006539

studies were identified (seven in total), and the results of these were somewhat mixed, with two reporting no improvements in safety (Marasinghe 2015). As a result, further research is essential prior to wide-scale implementation of such systems within care homes. This should follow guidance on the development of complex interventions (O'Cathain et al. 2019), and include qualitative research with healthcare, pharmacy and care home professionals, and residents. This will ensure development is collaborative, with clearly defined user roles and acceptability criteria. Furthermore, pilot studies with examination of both clinical and person-centred outcomes should be undertaken prior to wide-scale implementation. Challenges in implementation of CCDS in the care home setting should also be considered, including financial and workforce pressures (Hunt et al. 2020), the navigation of data protection requirements across organisational boundaries spanning primary, secondary and social care services (Central Digital & Data Office 2020), and low levels of digital maturity across the care home sector (QA Research 2021).

As outlined in Chapter Five, eMAR systems have the feasibility of providing novel information that is not routinely accessible to healthcare professionals conducting reviews, including information on the exact timing of administration. This is notable as this additional information may affect clinical decision making. For example, for time-sensitive medicines such as levodopa, it can be hypothesised that unidentified variations in the gap between doses may lead to inappropriate alteration of medicine regimens and dosage in an effort to manage symptoms, where these may have been adequately controlled with consistent timing of administration. This needs thorough evaluation through further research.

6.3.3 Development of data assets

The final recommendation pertains to the investment in, and development of data assets, to help facilitate some of the potential benefits previously discussed. Although over 300 care homes and over 9,000 individuals were included in the core dataset presented in Chapter Two, it was estimated that this represented less than 3% of all care homes and residents in England. However, as this thesis examined data from a single eMAR provider, further

augmentation of coverage of data may be achieved through the linkage of data across different eMAR systems. Meanwhile, secure linkage to other data sources such as electronic care planning records or healthcare records, for example using the methodology undertaken by the Secure Anonymised Information Linkage (SAIL) Databank (SAIL Databank [no date]), would greatly improve the richness of data available. This would enhance the ability for researchers to study outcomes of potentially inappropriate medicines use patterns – an area of research that has generally been lacking to date. For this to be possible, clearly defined data and interoperability standards need to be developed. This has become an increasing area focus within the NHS (Department of Health and Social Care 2018,2021), and includes the use of standardised nomenclature and codes, for example dm+d standards for the recording on medicines and devices (NHS Business Service Authority [no date]), as used in this data source.

The development of a secure central repository should be explored, considering guidance of the Data Ethics Framework (Central Digital & Data Office 2020). This includes continual evaluation and governance, as well as the development of clear and comprehensive metadata documentation so that users understand how the data was collected, the contents of fields, and any potential data quality issues (Central Digital & Data Office 2020). As noted in the limitations, the data source used in this thesis contained potential data quality issues, including evidence of a possible failure to record date of birth for some residents. Further research should be conducted to assess the reasons for such findings and verify these as true data quality issues. Furthermore, continual monitoring and improvement in data quality should be implemented.

6.4 CONCLUSION

In conclusion, through exploring a case study of dopaminergic medicines commonly used in Parkinson's disease (PD), this thesis has outlined some of the potential benefits of utilising eMAR data, both in research and for the development of clinical interventions. This research has also provided a novel insight into the use of dopaminergic medicines in care homes, particular with respect to the precise timing of doses, evaluation of which is not possible with paper-based system. Limitations of the data have been identified and addressed. The author suggests further research should be conducted exploring the outcomes associated with dopaminergic medicines use patterns in care homes presented in this thesis. Furthermore, the development of data assets should be prioritised to facilitate research, clinical monitoring, and the creation of complex clinical interventions.

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APPENDIX

APPENDIX 1: CARE HOME SERVICE PRIMARY SUPPORT REASON

The "Adult Social Care activity and Finance Report, England 2019-20: Reference Data Tables" workbook was downloaded from the NHS Digital website (NHS Digital 2020) and used under the Open Government Licence for public sector information (The National Archives 2021). The period for which this data covers if the financial year of 2019/20, spanning 1st April 2019 to the 31st of March 2020.

Worksheet T35 was used, which contained details of the number of individuals for which long term care support was provided, broken down by age bands of 18-64 and 65 years and over and the primary support reason. It is worth noting that activity levels were rounded to the nearest five in the data source. Furthermore, where activity levels were less than 5, these were suppressed in the dataset with the use of a *. This affected four records, which were excluded from the analysis.

To produce the visualisation presented in Figure 1.1, the primary support reasons were categorised as shown in Table A.1. The number and percentage of the total was calculated for each category of primary support reason across residential homes and nursing homes for age bands of 18-64 years and 65 years and over.

Table A.1: Categorisation of Primary Support Reasons

Category	Primary Support Reason
Learning Disability Support	Learning Disability Support
Mental Health Support	Mental Health Support
Physical Support	Physical Support: Access and Mobility Only
	Physical Support: Personal Care Support
Sensory Support	Sensory Support: Support for Visual Impairment
	Sensory Support: Support for Hearing Impairment
	Sensory Support: Support for Dual Impairment
Social Support	Social Support: Substance Misuse Support
	Social Support: Asylum Seeker Support
	Social Support: Support for Social Isolation/Other
Support with Memory and Cognition	Support with Memory and Cognition

APPENDIX 2: DATA FIELDS USED

Field names presented here are adaptations of the database field names, allowing improved readability for the purpose of this thesis.[15]

Table A.2: Data fields used in the analyses presented in this thesis

Field	Description
Administration ID	Unique ID for each administration either 1) required 2) attempted or 3) administered
Archive Status	Indicator to identify whether the individual (Resident ID) remains a resident of the care home, through recording as active (0) or archived (1)
BNF Category	Category into which the medicine is classified within the British National Formulary (BNF) (British National Formulary [no date]a)
Care Home ID	Pseudonymised, unique ID to identify distinct care homes
Date and Time of Administration Attempt	Date and time at which a medicine administration attempt occurred
Date Required	Date on which a medicine was scheduled to be administered or, where the medicine is not set as scheduled, the date on which medicine administration was attempted
Medicine Start Date	Date on which a medicine was started
Medicine Status	Indicator to identify whether medicines are 'Active' or 'Stopped'
Medicine Stop Date	Date on which a medicine was stopped
Postcode	Postcode district of care home; this was aggregated to postcode area level for the analysis presented in this thesis
Reason Not Given	The reason for not administering a medicine selected by the user, or NULL if the dose was administered, or 'Missing Unknown' where no record of attempt was made for a scheduled medicine dose
Resident ID (Primary key of Resident table)	Pseudonymised, unique ID to identify distinct individuals living within care homes

[15] The medicines table may also be used to record other items listed in the dictionary of medicines and devices (dm+d) NHS Business Service Authority. [no date]. *Dictionary of medicines and devices (dm+d)*. NHS Business Service Authority. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/dictionary-medicines-and-devices-dmd [Accessed: 14/09/2021]. using the eMAR system (e.g. catheters and spacers). Therefore, the term medicines is used to refer to any such dm+d item recorded via the eMAR system.

Table A.2 (continued): Data fields used in the analyses presented in this thesis

Field	Description
Resident Medicine ID (Primary key of Medicine table)	Pseudonymised, unique ID to identify distinct medicines prescribed to an individual
Scheduling Type	Field identifying whether medicine is 1) scheduled for regular administration at fixed times (regular medicines), 2) as needed ('as required' medicines), or 3) a combination of both
Stock Level	The quantity of the medicine remaining. This may be in number (e.g. tablets), or by another unit of measurement (e.g. ml)
Time Required	Time at which a medicine was scheduled to be administered or, where the medicine is not set as scheduled, the date on which medicine administration was attempted
Title	Title recorded for individual; this was used as a proxy for sex
VMP Name	Virtual Medicinal Product name. This is the standardised dm+d name given for a medicine that includes the generic name (i.e. non-brand), the strength, and the form of the medicine (NHS Business Service Authority [no date])
Year of Birth	Year of birth of individual; this was used to calculate age by subtracting from 2020

APPENDIX 3: CQC DATA

The CQC regulate and inspect health and care services. Through their website, they provide a monthly care directory in excel format, giving details of registered services in England (Care Quality Commission 2021a), which may be analysed by end-users under the Open Government Licence for public sector information (The National Archives 2021). This includes information such as the type of service provided, and the number of registered beds within care services, allowing data to be filtered to examine only services registered as care homes providing Adult Social Care services for older adults.

In this thesis, the care directory dated 4th of January 2021 was downloaded and used for information on the number of care homes and registered beds in English care homes (Care Quality Commission 2021a).

For the analysis of the geographical distribution of care homes and care home size compared to the core dataset presented in Chapter Two the following filters were applied:

- "Care Home?" (Column C) set as "Y"
- "Provider Inspection Directorate" (Column AN) set as "Adult social care".
- "Service user band - Older People" (Col DE) set as "Y"
- "Care home beds" (Column I) set as greater than or equal to 5

APPENDIX 4: CENSUS DATA

Office for National Statistics (ONS) data on the number of individuals living in care homes by age category and sex for the 2001 and 2011 Censuses was obtained from the Nomis browser (Office for National Statistics 2003,2013) and used under the Open Government Licence for public sector information (The National Archives 2021). The Query Data option was used to produce data for specific selections. These are outlined in the Table A.3. Totals were calculated for the number of individuals across all included Establishment Types for each age category and for each sex. For 2001, the age categories 85-89 and 90 and over were aggregated to allow for comparability across years.

Table A.3: Data fields selected in the Nomis browsers when retrieving census data (Office for National Statistics 2003,2013)

Selection Type	2001 Census Selections	2011 Census Selections
Geography	Countries – England only	Countries – England only
Establishment Type	Communal establishments: • Medical and care establishments - Local Authority - Nursing Home • Medical and care establishments - Local Authority - Residential Care Home • Medical and care establishments - Other - Nursing home • Medical and care establishments - Other - Residential care home	Communal establishments: • Medical and care establishment: Local Authority: Care home with nursing • Medical and care establishment: Local Authority: Care home without nursing • Medical and care establishment: Other: Care home with nursing • Medical and care establishment: Other: Care home without nursing
Age and Position	Age categories: • Total • Age 65 to 74 • Age 75 to 84 • Age 85 to 89 • Age 90 and over	Age categories: • Resident: Total • Resident: Age 65 to 74 • Resident: Age 75 to 84 • Resident: Age 85 and over
Sex	All, male and female	All, male and female

APPENDIX 5: DOPAMINERGIC MEDICATIONS

Table A.4 outlines the dopaminergic medicines identified and the categorisation of these by Virtual Therapeutic Moiety (VTM) and medicine type.

Table A.4: Categorisation of dopaminergic medicines

Medicine Type	VTM	VMP
Levodopa	Levodopa + Benserazide	Co-beneldopa 25mg/100mg capsules
		Co-beneldopa 25mg/100mg dispersible tablets sugar free
		Co-beneldopa 25mg/100mg modified-release capsules
		Co-beneldopa 12.5mg/50mg capsules
		Co-beneldopa 12.5mg/50mg dispersible tablets sugar free
		Co-beneldopa 50mg/200mg capsules
	Levodopa + Carbidopa	Co-careldopa 12.5mg/50mg tablets
		Co-careldopa 50mg/200mg modified-release tablets
		Co-careldopa 25mg/250mg tablets
		CARAMET® 25mg/100mg cr tablets
		Co-careldopa 25mg/100mg tablets
		Co-careldopa 10mg/100mg tablets
COMT	Entacapone	Entacapone 200mg tablets
Levodopa + COMT	Levodopa + Carbidopa + Entacapone	Stalevo® 150mg/37.5mg/200mg tablets
		Stalevo® 125mg/31.25mg/200mg tablets
		Stalevo® 50mg/12.5mg/200mg tablets
		Stalevo® 200mg/50mg/200mg tablets
		Stalevo® 75mg/18.75mg/200mg tablets
		Stalevo® 100mg/25mg/200mg tablets

Table A.4 (continued): Categorisation of dopaminergic medicines

Medicine Type	VTM	VMP
Dopamine agonist	Amantadine[16]	Amantadine 50mg/5ml oral solution sugar free
		Amantadine 100mg capsules
	Apomorphine	Apomorphine 50mg/10ml solution for injection pre-filled syringes
	Pramipexole	PRAMIPEXOLE 350microgram tablets
		MIRAPEXIN® 1.05mg modified-release tablets
		Pramipexole 180microgram tablets
		Pramipexole 88microgram tablets
		MIRAPEXIN® 520mcg modified-release tablets
		PRAMIPEXOLE 260microgram modified-release tablets
	Ropoinirole	ROPINIROLE 8mg modified-release tablets
		ROPINIROLE 4mg modified-release tablets
		Ropinirole 250microgram tablets
		ROPINIROLE 5mg tablets
		Ropinirole 1mg tablets
		ROPINIROLE 2mg modified-release tablets
		Ropinirole 500microgram tablets
	Rotigotine	Rotigotine 4mg/24hours patches
		Rotigotine 2mg/24hours patches
		Rotigotine 6mg/24hours patches
		Rotigotine 8mg/24hours patches
MAO-B inhibitor	Rasagiline	Rasagiline 1mg tablets
	Selegiline	Selegiline 10mg tablets
		Selegiline 5mg tablets

[16] Amantadine acts as both a dopamine agonist and a glutamate antagonist. As it is classified as a dopamine agonist in the British National Formulary (BNF), it has been included in this category for the purposes of this thesis British National Formulary. [no date]a. *Treatment Summary: Parkinson's disease*. National Institute for Health and Care Excellence. Available at: https://bnf.nice.org.uk/treatment-summary/parkinsons-disease.html [Accessed: 25/07/2021].